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PULMONARY COMPLICATIONS OF CARDIOSPASM*

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THE association of cardiospasm and respiratory symptoms has been recognized since the beginning of the nineteenth century. Not until relatively recent years, however, has attention been directed to the relation between cardiospasm and a variety of pulmonary diseases ranging from lung abscess to pulmonary fibrosis. Massive or repeated aspiration of the contents of a dilated, food-filled esophagus frequently causes significant pulmonary complications. It is the purpose of the present report to emphasize this relation and to stress the value of prompt recognition and treatment of the underlying cardiospasm in order to prevent serious pulmonary disease. To date 46 case reports of pulmonary disease complicating cardiospasm have been published. These, plus 17 new cases, totaling 63 in all, form the material for this investigation.

REVIEW OF LITERATURE

Credit for the first published description of cardiospasm probably belongs to Thomas Willis[1] of London, who in 1672 mentioned a patient with an enlarged esophagus treated by bougienage. Mikulicz[2] in 1882 first used the term "cardiospasm," and Einhorn[3] in 1888 suggested that the condition was due to non-relaxation rather than spasm of the cardiac sphincter. Hurst[4] in 1914, at the suggestion of Sir Cooper Perry, employed the term "achalasia." The etiology of cardiospasm remains obscure, and its discussion is not within the scope of this paper. Regardless of the underlying cause, cardiospasm produces marked dilatation of the esophagus above the point of spasm, causing filling to a variable degree with contaminated food, which decomposes. Not infrequently, — usually at night, — this material is spilled into the trachea and aspirated into bronchi and lungs, thereby causing pulmonary complications ranging in varying degrees of severity, some being fatal. Similar aspiration often accompanies carcinoma of the esophagus, esophageal diverticula and benign stricture, conditions that are not considered here.

Respiratory symptoms are commonly associated with cardiospasm. Nocturnal cough and dyspnea were present in 25 of 301 cases (7.6 per cent) of cardiospasm reported by Plummer and Vinson[5] in 1921. A later account by Vinson[6] increased this number to 49 out of 415 cases, an incidence of 11.8 per cent. Sturtevant[7] quotes Scally, von Bergman and Lindvall concerning the frequent association of cardiospasm and asthma; other authors[8-10] are in agreement.

Not so well recognized has been the direct causal relation between cardiospasm and its manifold pulmonary complications. Of the major textbooks in medicine or pathology, only Bockus' *Gastroenterology*[11] and Harrison's *Medicine*[12] mention this relation.

Perhaps the first mention of pulmonary complications in a case of diffuse dilatation of the esophagus was implied by Mermod[13] in 1887, when he remarked about a patient: "The general state grows better — vomiting and night cough continue — the physician in attendance appears to have an uneasiness with regard to the patient's chest." Thomas and Jewett[14] in 1926 described a case of cardiospasm complicated by infiltration of the entire right lung. Autopsy showed an aspiration pneumonia due to the spilling of cream into the right bronchial tree from a dilated food-filled esophagus. In the following year, 1927, Vinson[15] described a case of cardiospasm that resulted in lung abscess. A few scattered cases were reported individually until 1944, when Weens[16] described 5 instances of pulmonary complications in 15 cases of cardiospasm. He reviewed the literature and emphasized the occurrence of pulmonary complications, the signs and symptoms of which might be overshadowed by those of concurrent cardiospasm. Hawes and Soule[17] reported an additional 2 cases in 1945 and in 1949; Belcher[18] collected 29 cases from the literature[14-17, 19-24] and added 5 new cases. He recorded a total of 34 cases of cardiospasm (achalasia) with pulmonary complications, apply-

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ing the general term "dysphagia pneumonitis." After an exhaustive search of American and foreign medical publications through January, 1951, 12 total of 63 instances of cardiospasm with proved pulmonary complications forms the material for the following discussion.

TABLE 1. *Laboratory Data on 17 Cases of Cardiospasm with Pulmonary Complications.*

Case No.	Origin	Age	Sex	Chief Complaints	Chest X-Ray Findings	Remarks
1	N. Y. C. Dept. Health, Bureau of Tuberculosis	45	M	Dyspnea 6 yr.; pneumonia and pleurisy 2 yr. ago, with chronic cough since.	Infiltration in right upper and right middle lobes	Sputum negative for acid-fast bacilli
2	N. Y. C. Dept. Health, Bureau of Tuberculosis	37	M	Cough and vomiting since childhood, especially when reclining; hemoptysis once.	Consolidation in left upper lobe	Smear, culture and gastric washings negative for acid-fast bacilli
3	N. Y. C. Dept. Health, Bureau of Tuberculosis	51	F	"Bad cold" for 4 wk., ending in pneumonia	Infiltrations in left and right lower lobes	Sputum negative for acid-fast bacilli; previously received 10 deep x-ray treatments to mediastinum for "mass."
4	New York Hospital (Case No. 529,873)	56	F	5 yr. epigastric distress and vomiting; 3 wk. nightly cough with sputum and temperature elevation to 103°F.	Infiltration in right upper lobe from apex to 3rd rib; on admission infiltration extended to left upper and lower lobes after acute attack of aspiration.	Gastric washings and sputum cultures negative for acid-fast bacilli; in hospital acute attack of aspiration pneumonitis occurred.
5	New York Hospital (Case No. 404,150)	59	F	19 yr. dysphagia; 6 yr. ago, acute attack of chest pain, chills and fever following bout of vomiting	Fibrocalcific densities in left upper lobe; soft infiltration in apex of right upper lobe with pleural effusion	Culture of pleural effusion negative for acid-fast bacilli; gastrostomy performed for severe emaciation.
6	New York Hospital (Case No. 284,037)	42	F	16 yr. dysphagia and regurgitation; 8 yr. ago aspiration pneumonia; cardiospasm diagnosed; 7 yr. ago 16 mo. in TB hospital; sputum negative for *Myco. tuberculosis*; 6 yr. ago 3 bouts of pleurisy, sputum negative; 6 mo. cough, sputum and hemoptysis	Infiltration with small excavations in right upper lobe from subclavicular region to 3rd rib anteriorly	Sputum repeatedly negative for acid-fast bacilli during 16 yr. in which cardiospasm was present; spent 16 mo. in TB hospital; finally developed positive sputum years later. Autopsy revealed TB cavities in left lower, left upper and right upper lobes with caseous foci in all lobes and TB pneumonia and dilated esophagus with esophagitis.
7	Harlem Hospital (Case No. 175,667)	36	M	1 yr. cough and dyspnea; 6 mo. dysphagia; 2 wk. chills, fever and bloody sputum.	Consolidation of right lower lobe and marked hilar prominence due to cardiospasm	Sputum cultures negative for acid-fast bacilli
8	Bellevue Hospital	40	F	19 yr. dysphagia and regurgitation; 6 yr. ago hospitalized for TB, which was never proved.	Small excavations in left upper lobe; fibrotic infiltrates in right lung field.	Spent 1½ yr. in TB sanatorium; sputum consistently negative for acid-fast bacilli. TB nodes in neck found after 19 yr.
9	Bellevue Hospital	51	M	13 yr. dysphagia, regurgitation, vomiting and weight loss	Pneumonitis in both lower lobes	Esophagus perforated by an esophagoscope, resulting in a streptococcal mediastinitis and death; no autopsy; sputum negative for acid-fast bacilli.
10	Bellevue Hospital	58	M	2 yr. ago pneumonia, 1 wk. left-scapular pain and weight loss; no dysphagia or vomiting	Pneumonia in left upper lobe; eventually spread to right lower lobe.	Autopsy showed megaesophagus, esophagitis, chronic interstitial pneumonitis, actinomycosis, acute bronchitis and acute lobular pneumonia due to mineral oil.
11	Lenox Hill Hospital (Case No. 116,570)	51	M	5 yr. dysphagia; 6 mo. cough and regurgitation; 2 bouts of chills and fever.	Infiltration of dorsal segment of right lower lobe	No sputum examination; cardiomyotomy performed.
12	Lenox Hill Hospital (Case No. 29,485)	51	F	13 yr. dysphagia, pain and weight loss; 2 wk. cough, hemoptyses and chest pain	Heavy infiltrations in left upper lobe	No sputum examination
13	Lenox Hill Hospital (Case No. 76,899)	60	F	10 yr. ago cardiospasm diagnosed by x-ray; 3 yr. dysphagia; 2 mo. weight loss, cough, sputum	Dense infiltration in right upper, right middle and right lower lobes	No sputum examination
14	Lenox Hill Hospital (Case No. 81,047)	82	F	2 wk. dysphagia, cough, dyspnea	Diffuse infiltration in right upper lobe and near right hilum	No sputum examination
15	Lenox Hill Hospital (Case No. 109,286)	25	F	7 attacks of pneumonia in 12 yr.	Large area of density in right lower lobe	Sputum negative for acid-fast bacilli
16	Case of L. E. Siltzbach, M.D.	45	M	8 yr. dysphagia and vomiting; 6 days fever and right-chest pain	Lung abscess with cavitation in right upper lobe	Abscess unroofed with incision and drainage
17	Case of D. Ulmar, M.D.	30	M	7 yr. regurgitation, cough, expectoration; 5 wk. ago acute attack of pneumonia in bed after coughing bout.	Diffuse patchy bronchopneumonia of both lower lobes	No sputum examination

case reports[38-44] that were not included in Belcher's 34 cases have been found. In addition, 17 previously unpublished cases are presented here. The

Pertinent clinical, laboratory and pathologic data on 17 previously unpublished cases of cardiospasm with pulmonary complications are presented in

Table 1. The diagnosis of cardiospasm was established by barium study (criteria of Bockus[11] and Feldman[45], chest film (criteria of Weens[16] and Hurst and Bassin[46]) or esophagoscopy. Chest roentgenograms established the presence of pulmonary disease in all 17 cases.

Case Reports

Chronic Interstitial and Acute Lipoid Aspiration Pneumonia with Pulmonary Actinomycosis; Cardiospasm; Autopsy

Case 10. J. C., a 58-year-old man, entered the hospital in 1936 complaining of left-chest pain, loss of weight and weakness of 8 weeks' duration. He had recovered from pneumonia 2 years previously. The patient persistently denied symptoms suggestive of cardiospasm. Clinical and roentgen

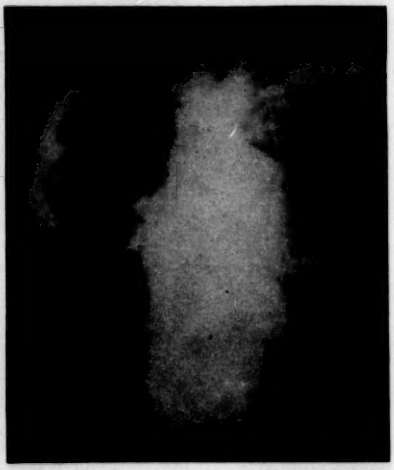

Figure 1. *Chronic Interstitial and Acute Lipoid Aspiration Pneumonia with Pulmonary Actinomycosis; Cardiospasm (Table 1, Case 10).*

X-ray film shows widespread pneumonia in left upper lobe.

evidence showed the presence of pneumonia (Figure 1), and a barium swallow revealed the presence of cardiospasm. Despite a gastrostomy the course was gradually downhill, the pulmonary involvement increased (Figure 2) in severity and the patient died. Present-day chemotherapeutic agents were not then available.

Autopsy revealed the characteristic changes of cardiospasm. The lungs were the site of a widespread chronic interstitial pneumonitis with involvement of all lobes. Histologic examination showed acute patchy purulent lobular pneumonia, chronic granulomas that contained numerous intracellular vacuoles and macrophages shown to contain mineral oil by special studies and small circumscribed abscesses of recent origin in the center of which *Actinomyces bovis* was present. The autopsy findings in this case have been reported by Graef.[47] The tendency of mineral oil to float on a liquid mass probably facilitated its regurgitation in this case. The origin of the actinomyces, which were probably terminal invaders, may well have been the buccal cavity, introduction into the lungs having occurred through aspiration.

Aspiration Pneumonia of Right Lower Lobe; Cardiospasm

Case 11. A 51-year-old woman was admitted because of recurrent cough, regurgitation, chills and fever of 6 weeks' duration. For 5 years she had a sensation of obstruction on swallowing. Physical examination revealed rales at the right base. A chest roentgenogram showed an infiltration in the right-lower lung field (Figure 3). The esophagram (Figure 4) showed cardiospasm. After the subsidence of the pneumonitis, cardiomyotomy (Heller's operation) was performed.

Pneumonitis, Left Upper Lobe; Cardiospasm

Case 12. A 51-year-old woman was admitted with complaints of cough, chest pain and hemoptysis of 2 weeks' duration. For 13 years she had had dysphagia, regurgitation, epigastric pain and weight loss. Physical examination showed malnourishment. There were no abnormal chest signs, but the roentgenogram showed a dense area of infiltration in the left upper lobe. An esophagram showed cardiospasm. The pneumonia resolved promptly on conservative therapy, and the patient was discharged with instructions to lavage her

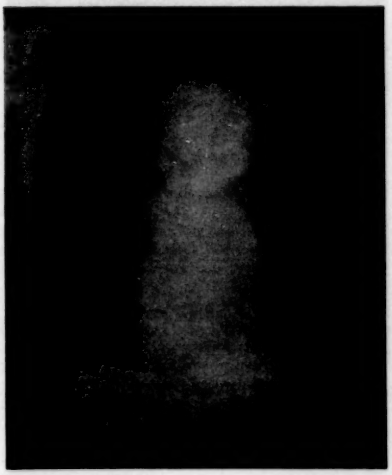

Figure 2. *Roentgenogram of Chest 2 Days Prior to Death, Showing Diffuse Spread in the Lower Half of the Right Lung Field (Table 1, Case 10).* (*Courtesy: J. Burns Amberson, Jr., M.D., Chest Service, Bellevue Hospital.*)

esophagus before retiring each night. During a follow-up period of 10 years pneumonia did not recur.

Lung Abscess, Right Upper Lobe; Cardiospasm

Case 16. A 45-year-old man complained of fever, right-upper-chest pain, cough and expectoration of foul sputum of 6 days' duration. For 8 years he had had substernal pain relieved by self-induced vomiting. An x-ray film of the chest (Figure 5) showed a large right-upper-lobe cavity and an esophagram revealed a widely dilated esophagus filled with food to the right of the sternum. Incision and drainage of the lung abscess was carried out, and after several months

of tube drainage the patient recovered and resumed his work. To date, the cardiospasm remains unchanged and the patient refuses further surgery.

Discussion

Incidence

Of the 64 cases of cardiospasm with pulmonary complications reviewed or reported here, 27 (42.9 per cent) were in men, 35 (55.5 per cent) were in women and the sex of 1 patient was unknown. The sex incidence of cardiospasm is about equal.[9, 48]

It is impossible to be certain of the age of onset of cardiospasm in the 63 patients reported here. The age range at the time of diagnosis was from six to eighty-two years; the average age was 40.5 years. According to Vinson,[49] most cases of cardiospasm occur in the third and fourth decades of life.

Figure 3. *Aspiration Pneumonia, Right Lower Lobe; Cardiospasm (Table 1, Case 11).*
Roentgenogram shows infiltrate in right lower lobe.

Presenting Complaint

In 25 (39.5 per cent) of the 63 cases, initial presenting complaints were referable to the pulmonary complication rather than to the esophageal disease. Cough, sputum, hemoptysis, fever and chest pain were common complaints; symptoms referable to cardiospasm were either not present ("silent dysphagia") or were subordinate to the respiratory symptoms. In most of the remaining 38 cases (60.5 per cent), symptoms such as dysphagia, regurgitation and vomiting were complained of initially. Eleven patients noted the simultaneous onset of symptoms caused by the cardiospasm and its pulmonary complications. In 27 patients the symptoms of cardiospasm antedated the pulmonary symptoms for periods ranging from two months to thirty-two years, the average interval being 7.8 years.

It is significant that more than one third of the patients reported here complained initially of symptoms referable to the pulmonary complications of cardiospasm rather than of symptoms directly due to the disease itself. Unexplained pulmonary suppuration or infiltrations, therefore, should always indicate a study of the esophagus.

Pathological Data

Autopsied cases. Autopsy was performed in only 9 of the 63 cases. Eight of these 9 patients died after protracted chronic illnesses; one patient died suddenly after massive aspiration of esophageal contents. In all instances megaesophagus was observed. The pulmonary findings are summarized in Table 2.

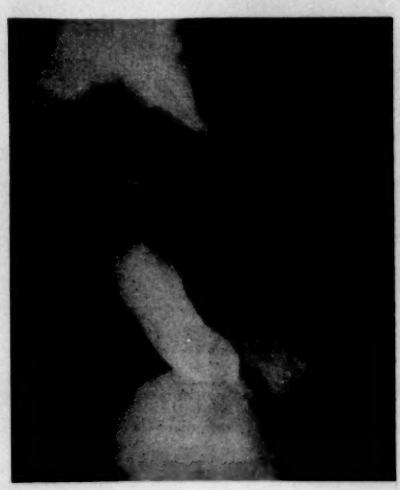

Figure 4. *Esophagram from Case 11 (Table 1), Showing Typically Dilated Esophagus.*

Pulmonary Lesions Encountered

As evidenced by all available clinical, laboratory and roentgenographic data, it appears that in most

of the cases discussed here the pulmonary complications of cardiospasm were the result of repeated aspiration. Usually the course was long and protracted, and the cumulative effect of repeated small aspirations may be logically inferred. This, however, is not always the case. Hurst[10] reported the case of a patient who had not complained previously of respiratory symptoms. While the patient was bending forward, death from asphyxia occurred as a result of massive aspiration. In our Case 4 (Table 1), difficulty in swallowing supper was followed by a wakeful night of choking and coughing. A chest film made the next day revealed

FIGURE 5. *Lung Abscess, Right Upper Lobe; Cardiospasm (Table 1, Case 16).*

X-ray film shows rounded cavity in right upper lobe, with dilated food-filled esophagus adjacent to right-mediastinal and cardiac border. (Courtesy: L. E. Siltzbach, M.D., New York.)

pneumonia of the left lower and upper lobes that was presumably the result of aspiration.

The pulmonary complications encountered in the presence of cardiospasm are summarized in Table 3. Fibrotic or nonspecific "infiltrations" accounted for 44.8 per cent of the pulmonary lesions. Lung abscess was present in 12.5 per cent of the 63 cases. In 765 cases of lung abscess collected from the literature[80-84] no cause was apparent in 137 instances (17.9 per cent). It is possible that some of these lung abscesses may have been the result of an unsuspected (and therefore unsought-for) "silent dysphagia." Of the present series of cases, 12.5 per cent showed pneumonia, 7.8 per cent pulmonary tuberculosis, 6.4 per cent bronchiectasis, 4.8 per cent atelectasis and 4.8 per cent (3 cases) oil-aspiration pneumonia. In 1 of these, our Case 10, mineral oil was demonstrated in the lungs at autopsy. This

TABLE 2. *Pulmonary Findings in 9 Autopsied Patients with Cardiospasm and Pulmonary Complications.*

ORIGIN OF CASE	PULMONARY FINDINGS AT AUTOPSY
Reeke[37]	Bronchiectasis and acute pneumonia, both lower lobes
Hurst[10]	Massive aspiration, food filling all main bronchi and occluding glottis
Mallory[31]	Suppurative aspiration pneumonia, right base; incidental carcinoma of esophagus.
Robson and Wilkinson[33]	Bronchopneumonia, right middle lobe
McKinney[41]	Empyema, atelectasis and bronchopneumonia, bilaterally
Thomas and Jewett[34]	Large posterior mediastinal abscess and pneumonia due to aspiration of cream, right lung
Denis, Garre and Latienda[35]	Tuberculous infiltrations and caseation, right lung; calcified nodes, left hilum.
Case 6	Tuberculous cavities in left lower, left upper and right upper lobes with caseous foci in all lobes and generalized tuberculous pneumonia
Case 10 (Graef[47])	Widespread chronic interstitial pneumonitis; acute, patchy, purulent lobular pneumonia; chronic granulomas with numerous intracellular vacuoles and macrophages containing mineral oil; abscesses containing *Actinomyces bovis*.

and 2 other cases reported argue against the administration of mineral oil to patients with cardiospasm. Pleural effusion, asphyxia due to massive aspiration and pneumothorax accounted for the remaining cases (6.4 per cent). Belcher[18] has discussed the pathogenesis of these pulmonary lesions and relates them to aspiration, especially during sleep. Our conclusions are in agreement.

Affected Lobe

It is probable that aspiration due to cardiospasm occurs most often at night. During this time protective cough reflexes are dulled by sleep. The anatomy of the bronchi is such that in the recumbent position the right main bronchus assumes an almost vertical, and therefore a particularly

TABLE 3. *Pulmonary Complications.*

TYPE	No.	PERCENTAGE
Nonspecific infiltrates (fibrosis)	28	44.8
Pneumonia	8	12.5
Lung abscess	8	12.5
Pulmonary tuberculosis	5	7.8
Bronchiectasis	4	6.4
Atelectasis	3	4.8
Oil-aspiration pneumonia	3	4.8
Pleural effusion	2	3.2
Occlusion of bronchi with asphyxia	1	1.6
Pneumothorax	1	1.6
Totals	63	100.0

vulnerable, position. In the 28 cases in which specific lobe involvement is known to have been present, the right upper lobe was involved 12 times, the right lower lobe 8 times, the right middle lobe

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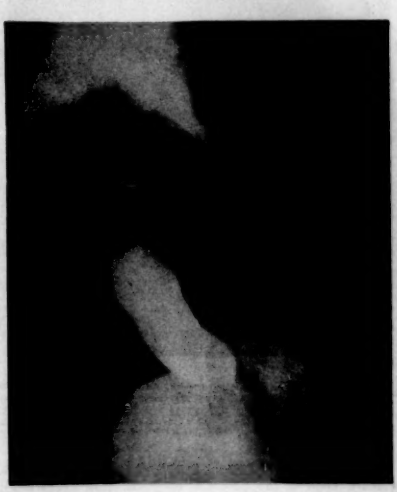

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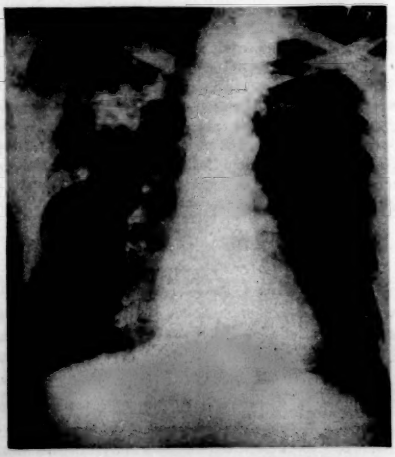

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vulnerable, position. In the 28 cases in which specific lobe involvement is known to have been present, the right upper lobe was involved 12 times, the right lower lobe 8 times, the right middle lobe

5 times and the left upper lobe 3 times. In 52.2 per cent of the cases in this series there was solitary involvement of the right lung; in 6.4 per cent, the left lung; in 30.2 per cent both lungs were involved. The remaining 11.2 per cent of cases were unclassified with regard to side of involvement. These findings are in essential agreement with those of Pinchin and Morlock,[55] who found that the right lung is affected by pulmonary abscess 2.5 times more commonly than the left.

Acid-Fast Bacilli and Cardiospasm

Tuberculosis is another complication of cardiospasm. Seven cases have been reported.[5, 16, 35, 37, 38] For lack of sufficient clinical information, 4 of these cases[5, 16] could not be included in our series. The sputum or gastric washings in 29 of the 63 cases reported here were examined for acid-fast bacilli. Of these 29 examinations, 21 were negative. In 5 cases[2, 3, 8, 55, 56] an acid-fast, nonpathogenic, saprophytic bacillus was isolated. That this organism was not the tubercle bacillus was reasoned because of atypical tuberculin tests and uncharacteristic growth and morphology. Cummins and Williams[22] isolated such an acid-fast organism from a patient. This organism was able to survive for long periods of time in the body and produced septic, easily-healed lung lesions rather than caseation. Treatment of the cardiospasm terminated repeated insults to the lungs by aspirated material and was followed by prompt resolution of the pulmonary lesions. Rothstein and Pirkle[39] and Cummins and Williams[22] isolated strains of acid-fast bacilli from patients with cardiospasm that were nonpathogenic to guinea pigs. Similarly, Pinner[56] described 16 strains of acid-fast bacilli capable of producing benign self-healing lesions in guinea pigs and stated that such organisms may ultimately become virulent. The relation is suggestive and presents an argument in favor of the early treatment of such lesions.

Tubercle bacilli were isolated in 2 of our cases (Table 1, Cases 6 and 8). In these cases, however, repeated sputum examinations had been negative for periods of sixteen and nineteen years respectively. In view of the general debility and the frequency of chronic lung disease associated with the disorder, it is surprising that more patients with cardiospasm do not develop tuberculosis. Patients with cardiospasm and pulmonary infiltration have been known to spend months or years in sanatoriums, even in the absence of bacteriologically demonstrable tuberculosis. Schmidt's case[43] and our Cases 6 and 8 are examples. Had the relation between cardiospasm and pulmonary disease been considered, such periods of potential or real exposure to tuberculosis might have been avoided. Patient 6 spent sixteen months in a tuberculosis sanatorium with negative sputum reports but later developed pulmonary tuberculosis. Treatment of her cardiospasm sixteen years previously might have prevented this outcome.

Summary

Cardiospasm complicated by pulmonary disease has been studied in 63 cases, 17 of which are reported here for the first time. It is evident that the aspiration of material from the dilated food-filled esophagus, especially at night, may cause serious pulmonary lesions such as pneumonia and lung abscess — or even sudden asphyxia. These lesions cannot be expected to respond permanently to therapy unless attention is directed toward the elimination of the fundamental lesion, the cardiospasm itself.

Cardiospasm is a treatable disease.[11, 57-60] The present study indicates the desirability of early diagnosis and definitive therapy.

The association of cardiospasm and pulmonary disease due to aspiration is sufficiently common to warrant its re-emphasis in this report. It is urged that the esophagus always be examined when pneumonia, nonspecific pulmonary infiltration, lung abscess or pulmonary lesions of obscure etiology occur.

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CARCINOMA OF THE OVARY: CLINICAL AND PATHOLOGICAL EVALUATION*

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A REPORT of the cases of ovarian cancer seen at the Massachusetts General Hospital from 1901 through 1934 showed the five-year survival rate to be only 15.5 per cent.[1] In order to evaluate the results of more recent therapy and to search for a means of improving the results of treatment, the cases observed from 1935 to 1943 have been reviewed. An attempt was also made to correlate the pathological findings with the clinical course. Sixty-seven cases of primary ovarian malignant disease were found. Recognized endocrine tumors were excluded.

Seventy-nine per cent of the patients were between the ages of forty and seventy. The peak age of incidence was in the sixth decade and the range from twenty-two to seventy-six. The patients did not differ significantly from the general population with respect to marriage or pregnancies.

The symptoms, such as pain, abdominal mass, or swelling, were due to the presence of the tumor or to its pressure on adjacent structures. Sixteen patients experienced abnormal vaginal bleeding; 10 per cent of these were postmenopausal. In the absence of endometrial metastases, hormonal activity of the tumor or stimulation of the ovary by the tumor must be postulated (Table 1). As the tumor must attain a modest size before symptoms develop, the duration of symptoms is not an accurate measure of the duration of the disease. The duration ranged from a few weeks to two years.

TABLE 1. *Symptoms of Carcinoma of the Ovary.*

SYMPTOM	NO. OF CASES	PERCENTAGE	NO. OF PATIENTS SURVIVING 5 YEARS OR MORE
Pain	38	57	14
Swelling or mass	41	61	9
Bleeding	16	24	5
Vomiting	15	22	6
Constipation	7	10	—
Urinary symptoms	6	9	1
Fatigue, dyspnea	2	3	1
No symptoms (tumor found incidentally)	2	3	—

There was no detectable difference in this respect between the group as a whole and those who survived five years or more.

The prominent physical finding was an abdominal or pelvic mass and was present in 60 of the 67 cases. Tenderness of the lower abdomen was a significant finding in only 3 patients. Six patients

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had ascites; none of these lived five years. No other finding consistently altered the prognosis.

Eight patients were peritoneoscoped; in 3 this was the only procedure. Ten patients had a laparotomy at which only a biopsy was done. One of these, a patient with a low-grade serous cystadenocarcinoma, lived ten years. She received extensive x-ray therapy. The surgeon realized that the tumor was incompletely removed in 24 patients. Three of these lived over five years, 2 having received x-ray treatment. The patient who received no therapy lived eight years but died of a low-grade pseudomucinous cystadenocarcinoma. In 27 cases all of the tumor was thought to have been removed at the time of operation. Total hysterectomy and bilateral salpingo-oophorectomy were usually included in this procedure. Fifteen of these 27 patients lived five years. Five patients died after operation of the 54 subjected to laparotomy, all of whom had advanced carcinoma.

Forty-eight of the 67 patients received one or more courses of x-ray treatment (Table 2). The amount

TABLE 2. *Treatment in 67 Cases.*

TYPE OF OPERATION	TOTAL GROUP		5-YEAR SURVIVALS	
	NO. OF CASES	X-RAY TREATMENT	NO. OF CASES	X-RAY TREATMENT
Complete removal	27	19	15	10
Partial removal	24	18	3	2
Biopsy only	10	6	1	1
No operation	6	5	—	—

of radiation per course, measured as skin dose, varied from 2000 to 7500 r. Nineteen of 27 "complete-removal" patients received x-ray therapy. Of the 15 who survived five years, 66.6 per cent had received x-ray treatment. Three of the 4 patients in whom gross tumor remained at operation and who survived five years received x-ray therapy.

One patient, previously mentioned, who had a laparotomy and biopsy and who had a serous cystadenocarcinoma lived ten years but died of the carcinoma. After operation she received 1800 r through each of four portals; two years later she received 2700 r through each of three portals. The tumor was reduced in size after each course. In the last eight years of her life multiple paracenteses were done, as the condition of the skin prevented further radiation. Two patients who had partial removal of the tumor received 1800 r through each of four portals. One patient is living at the end of nine years; the other died after six years. In such cases it appears that x-ray therapy may be helpful and may even have a curative effect (Table 2). Marks and Wittenborg[3] emphasize its value.

Most tumors were cystic; a few were entirely solid, and may of the cystic tumors had solid foci. Histologically, the tumors were grouped as pseudomucinous, serous or unclassified (Table 3). The pseudomucinous tumors had tall, columnar, mucus-containing epithelium, but areas of the tumor were less well differentiated. The serous group was more heterogeneous, containing tumors in which the epithelium was low cuboidal with clear cytoplasm and tumors with taller epithelium containing cells

TABLE 3. *Histologic Classification.*

TYPE OF TUMOR	TOTAL NO. OF PATIENTS		FIVE-YEAR SURVIVALS	
	NO.	PERCENTAGE	NO.	PERCENTAGE
Pseudomucinous	16	23.9	4	25.0
Serous	35	52.2	11	31.4
Undifferentiated	12	17.9	2	16.7
Fibrosarcoma	3	4.5	2	66.7
Teratoma	1	1.5	—	

resembling tubal or endometrial-lining cells. No tumors of the endometrial type were thought to have arisen from a focus of endometriosis. The unclassified group consisted of tumors that fitted into neither of the above groups and whose epithelium appeared as sheets or as nests of poorly differentiated cells. Four other tumors, — three fibrosarcomas and one teratoma, — occurred in the series. Three fibrosarcomas in so small a group is unusual. Novak[2] gives the usual incidence as 1 sarcoma to each 40 carcinomas encountered.

The serous carcinomas showed a greater tendency to be bilateral (Table 4). Five of the 32 patients with bilateral tumors survived five years.

The tumors were graded on the basis of frequency of mitoses, degree of invasiveness, pleomorphism of

TABLE 4. *Laterality of Tumors.*

TYPE OF TUMOR	BILATERAL	UNILATERAL	UNKNOWN
Pseudomucinous	5	8	3
Serous	19	12	4
Undifferentiated	7	5	
Fibrosarcoma	1	2	
Teratoma	0	1	
Totals	32	28	7

cells, amount of secretion in the cells and degree of piling up to epithelium in the cysts. On these criteria a prognosis of good, fair or poor was made. The tumors that appeared to be slowly growing and well differentiated were less lethal, and the undifferentiated tumors were more malignant. Patients with cystic tumors had a more favorable prognosis than the cystic-solid or solid types.

DISCUSSION

In this group of patients 28.4 per cent lived five years after cancer was diagnosed. The exclusion of the fibrosarcomas decreases the figure to 26.6 per

cent. We attribute this improvement of 11 per cent over results obtained previously[2] to more aggressive surgical treatment and the use of x-ray therapy. Earlier diagnosis with earlier treatment may have been a factor in improving the results, but many of these patients had relatively far advanced disease.

The proper therapy for ovarian cancer in operable cases is surgical removal of the tumor, the other ovary, both tubes and the uterus, including the cervix. X-ray treatment is certainly indicated if the tumor has been incompletely removed. It appears to have been of definite benefit in this group. If cancer is thought to have been completely removed, the decision concerning radiation must be made on the basis of the individual case.

The attempt to correlate histologic appearance with survival rate was only moderately successful but is comparable to other series in this respect.[4] Of the cases given a "good" prognosis 61.5 per cent lived for five years. The only patients who survived five years after partial removal of the tumor were in the "good" prognosis group. All of those who were given a "poor" prognosis on the basis of histologic examination of the tumor and who survived five years had complete removal of the tumor. The "fair" and "poor" groups did not differ significantly.

Carcinoma of the ovary produces no characteristic early symptom. The commonest symptoms are those due to the pressure of the growing mass, but unfortunately the tumor is in a location in which considerable expansion can occur before the patient is aware of its presence. The presenting complaint of either swelling or an abdominal mass was noted in 61 per cent of these patients. The disease is often relatively advanced when the patient is first seen. The possible significance of vague lower-abdominal discomfort or pressure symptoms and mild urinary symptoms must be appreciated by the physician. Ovarian carcinoma may be mistaken for uterine fibroids, as the latter diagnosis was initially made in four cancer patients. One patient followed for twenty years with a diagnosis of uterine fibroids was found at operation to have fibroids and inoperable carcinoma. Vaginal bleeding occurred as a symptom in 16 of our patients, and this emphasizes the fact that ovarian carcinoma must be considered in the search for an explanation of such bleeding. A carefully taken history and a complete physical examination may detect earlier lesions than are usually observed. The rectal and pelvic examinations are essential and must be more widely utilized in the search for early cancer of the pelvic organs. They should be a part of all general physical examinations made in the office and certainly should be made on all patients admitted to the hospital. One of the patients in this series was admitted to another hospital because of a fractured patella three months before her admission to this hospital. Our admission examination revealed a 15-cm. pelvic mass, which should have been detected earlier.

Summary

Sixty-seven cases of malignant ovarian tumors were reviewed. The five-year survival rate was 28.4 per cent, which shows improvement over the previous series. A correlation of the histologic picture with the survival rate was fairly successful. At present the only means of improving the survival rate is to carry out more complete and thorough examination on apparently healthy women as well as on those with symptoms.

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THE INCIDENCE OF HYPERTENSION IN MITRAL STENOSIS*

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FORTY-TWO years ago Gibson,[1] in writing about the arterial pressure in mitral stenosis, stated: "It is often below the normal but even more frequently above it." In 1912 Cowan and Fleming[2] discussed the association between mitral stenosis and renal fibrosis and concurred with Gibson's statement. Several years later, Coombs[3] also stated that in mitral stenosis a "raised pressure is not uncommon." He reported that 3 of 16 patients with mitral stenosis had hypertension. Since then, several conflicting reports concerning the incidence of hypertension in mitral stenosis have appeared in the literature.

The purpose of the present study is to reinvestigate the association of hypertension and mitral stenosis. A series of 517 cases of mitral stenosis were therefore reviewed. The diagnosis was established by means of history, physical findings, electrocardiogram and x-ray films when available, and in some patients by post-mortem confirmation. Any cases in which the available data were insufficient to establish the diagnosis were not included. All cases of rheumatic heart disease that involved other valves in addition to the mitral valves were excluded because of the known effect of such involvement on the blood pressure. The criteria of hypertension employed in our study are a systolic pressure of 150 or over and a diastolic level of 90 or above. These levels coincide with those used in previous reports on this subject. As controls we used 2000 consecutive admissions to the Boston City Hospital. The blood pressures we have used in both the mitral-stenosis and control series are averages of several readings recorded during the period of hospitalization.

TABLE 1. *Age Groups, Sex Distribution and Incidence of Hypertension in 517 Cases of Mitral Stenosis.*

AGE GROUP	TOTAL NO. OF MALES	TOTAL NO. OF MALES WITH HYPERTENSION	PERCENTAGE OF MALES WITH HYPERTENSION	TOTAL NO. OF FEMALES	TOTAL NO. OF FEMALES WITH HYPERTENSION	PERCENTAGE OF FEMALES WITH HYPERTENSION
yr.						
11–15	13	1	7.6	20	0	0
16–25	17	2	11.7	49	1	2.0
26–35	36	2	5.6	59	5	8.4
36–45	32	11	34.3	68	10	14.7
46–55	54	7	12.9	83	26	31.3
56–65	28	8	28.5	36	15	41.6
66–75	3	1	33.3	16	12	75.0
Above 75	2	1	50	1	1	100.0

TABLE 2. *Age Groups, Sex Distribution and Incidence of Hypertension in 2000 Control Cases.*

AGE GROUP	TOTAL NO. OF MALES	TOTAL NO. OF MALES WITH HYPERTENSION	PERCENTAGE OF MALES WITH HYPERTENSION	TOTAL NO. OF FEMALES	TOTAL NO. OF FEMALES WITH HYPERTENSION	PERCENTAGE OF FEMALES WITH HYPERTENSION
yr.						
11–15	27	0	0	10	0	0
16–25	86	3	3.4	177	5	2.8
26–35	83	7	8.4	139	5	3.5
36–45	168	34	20.2	147	22	14 9
46–55	174	49	28.1	124	46	37.0
56–65	203	85	41.3	148	74	50.0
66–75	170	64	37.6	156	86	55.1
Above 75	85	39	45.8	103	62	60.0

DISCUSSION

In our series of 517 cases of mitral stenosis, the age range was from eleven to over seventy-five years. The majority of the patients were below forty-five years of age. However, a surprisingly large number were above this age. We found that 223 patients (43.1 per cent) were above forty-five years of age. In Levine and Fulton's study[4] only

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159 patients (20.9 per cent) were over forty-five years of age in a group of 762 cases.

Of the 517 cases of mitral stenosis that we reviewed, a total of 19.9 per cent had hypertension. This includes all age groups and both sexes. The control group of comparable age and sex showed an incidence of 29.1 per cent with an elevated blood pressure.

In those patients with mitral stenosis below forty-five years of age, 10.9 per cent exhibited hypertension, whereas the control group of the same age distribution showed a 9.1 per cent incidence of high blood pressure.

Above the age of forty-five, 31.9 per cent of the mitral-stenosis group had an elevated pressure, but 43.4 per cent of the control series in this age group had hypertension.

Except for the younger age group, our results indicate a decreased frequency of hypertension in patients with mitral stenosis. In those patients below the age of forty-five, the incidence is essentially the same as in the control group.

The incidence of hypertension obtained in the various age groups in our study followed fairly closely the figures arrived at by Horns.[5] In his series of 144 autopsied cases of mitral stenosis, he found an incidence of hypertension of 23.6 per cent in the entire group, as compared with 21.6 per cent in his control series of 288 cases. In those over the age of forty-five the incidence of hypertension was 30 per cent, and in the control group of the same ages the incidence was 31 per cent. Below the age of forty-five, the patients with mitral stenosis had an incidence of hypertension of 13 per cent, whereas the control group had a 6 per cent incidence of high blood pressure. Horns felt that his series justified at least a "skeptical attitude" toward the concept of a greater frequency of hypertension in patients with mitral stenosis. Brumm and Smith[6] reported on 1925 patients of all ages with mitral stenosis in whom there was a 2.3 per cent incidence of high blood pressure. The results of their study showed the lowest incidence of hypertension in association with mitral stenosis of any of the papers we have reviewed. On the other hand, Boas and Fineberg[7] studied 135 cases of mitral stenosis of all age groups and reported an incidence of hypertension of 29 per cent. Of their 135 patients 67 were over the age of forty, and 55 per cent of these had hypertension. In their large control group, unselected for age and sex, 11 per cent had hypertension. A comparison of this 11 per cent incidence of hypertension in their controls with the figures for the groups above and below the age of forty revealed a markedly increased incidence of hypertension in patients with mitral stenosis. In the previously mentioned work by Levine and Fulton,[4] they found 92 cases (58 per cent) with hypertension in a group of 159 patients over the age of forty-five with mitral stenosis. Their conclusion was that "with advancing age patients with mitral stenosis have vascular hypertension with much greater frequency than the average population." They offered two possible explanations for the association of mitral stenosis and hypertension. In the first place, it was postulated that the causative agent of mitral stenosis also produces generalized vascular disease, which may terminate in arteriosclerosis and hypertension. Secondly, patients who develop rheumatic heart disease may have a "vulnerable vascular system" predisposing them, in addition, to hypertension. Below the age of forty-five the patients

TABLE 3. *Incidence of Hypertension in Entire Group.*

	Total Group		Under Age of 45		Over Age of 45	
	Mitral stenosis	Control	Mitral stenosis	Control	Mitral stenosis	Control
Horns						
No. of cases	144	288	53	106	91	182
No. with hypertension	34	62	7	6	27	56
Percentage with hypertension	23.6	21.6	13	6	30	31
Roseman and Wasserman						
No. of cases	517	2000	294	837	223	1163
No. with hypertension	103	581	32	76	71	505
Percentage with hypertension	19.9	29.1	10.9	9.1	31.9	43.4

TABLE 4. *Incidence of Hypertension in Females with Mitral Stenosis.*

	Total Group		Under Age of 45		Over Age of 45	
	Mitral stenosis	Control	Mitral stenosis	Control	Mitral stenosis	Control
No. of cases	332	1004	196	473	136	531
No. with hypertension	70	300	16	32	54	268
Percentage with hypertension	21.1	29.9	8.2	6.8	39.7	50.5

of Levine and Fulton with mitral stenosis tended to have a blood pressure lower than normal. This latter finding was not substantiated by either our results or those obtained by Horns[5] in his series of autopsied cases.

It has been a general impression that hypertension is more common in females with mitral stenosis than in males. It is also thought that mitral stenosis in itself is more frequent in females. Levine[4] found twice as many females with mitral stenosis as males, and of those with hypertension the incidence was even higher in the female than in the male (5:1). In Fishberg's book[3] there is also a statement to this effect. Likewise, in our study mitral stenosis was found to be more common in females than in males (1.8:1). However, the association of mitral stenosis and hypertension in the females of our series was approximately the same (2.1:1) as in males.

In our group of 332 female patients of all ages with mitral stenosis, we found that 70 (21.1 per cent) had hypertension. This was appreciably less than the female control group of 1004, in which there was a 29.9 per cent incidence of hypertension. In this group of 332 there were 136 patients over the age of forty-five, of which 54 (39.7 per cent) had hypertension. This again was less than our control figure of 50.5 per cent of females with hypertension but without mitral stenosis in this age group.

There were 185 males of all ages with mitral stenosis, of whom 33 (17.8 per cent) had hypertension. The control group of males, consisting of 996 cases, revealed an incidence of hypertension of 28.2 per cent. Again, the frequency of high blood pressure was greater in the control group. Over the age of forty-five, 17 (19.5 per cent) males out of a group of 87 with mitral stenosis showed an elevated pressure, whereas the controls in this age division had a 37.5 per cent incidence of hypertension. As in the female group, the frequency of hypertension seems to be less in patients over the age of forty-five if mitral stenosis is present.

The validity of our controls may be subject to question because all were hospital patients. In view of this, it is possible that the incidence of hypertension in this group is higher than in a general nonhospitalized population. We therefore have compared our control figures with those of Master,[9, 10] who summarized the blood-pressure readings in nearly 15,000 men and women, all of whom were industrial workers, residents of homes for the aged or general hospital admissions. From his data Masters calculated that 41 per cent of the male population and 51 per cent of the female population over the age of forty would be expected to have high blood pressure if the figure of 150/90 is regarded as hypertension. Our control figures of hypertension above the age of forty-five (male, 37.5 per cent; female, 50.5 per cent) are thus very similar to Master's results. We therefore consider our control group to be valid.

TABLE 5. *Incidence of Hypertension in Males with Mitral Stenosis.*

	TOTAL GROUP		UNDER AGE OF 45		OVER AGE OF 45	
	MITRAL STENOSIS	CONTROL	MITRAL STENOSIS	CONTROL	MITRAL STENOSIS	CONTROL
No. of cases	185	996	98	364	87	632
No. with hypertension	33	281	16	44	17	237
Percentage with hypertension	17.8	28.2	16.3	12.1	19.5	37.5

SUMMARY

A study was made of the incidence of hypertension in 517 patients with mitral stenosis of all age groups and both sexes, 2000 consecutive subjects of comparable age and sex distribution being utilized as controls.

In the 517 cases of mitral stenosis there was a 19.9 per cent incidence of hypertension; in the control group of 2000 patients 29.1 per cent had high blood pressure.

Above the age of forty-five 31.9 per cent of the mitral-stenosis group had an elevated pressure, but 43.4 per cent of the control series in this age group had hypertension.

Seventy (21.1 per cent) females of all age groups had hypertension in the group of 332 females with mitral stenosis: in the control group of 1004 females there was an incidence of hypertension of 29.9 per cent.

Over the age of forty-five, 54 (39.7 per cent) females with mitral stenosis had elevated pressures as compared with 50.5 per cent of the controls.

Of 185 males of all ages with mitral stenosis, 33 (17.8 per cent) had hypertension. The control group of males revealed 28.2 per cent hypertension.

Seventeen (19.5 per cent) out of a group of 87 males with mitral stenosis showed an elevated pressure, whereas the controls exhibited an incidence of 37.5 per cent hypertension.

In general, our results tend to corroborate those of Horns.[5] It appears from our study that the incidence of hypertension in patients with mitral stenosis, in all age groups and in both sexes, is not greater than that occurring in the general hospital population. This is in contrast to the general belief that hypertension is more common in

patients with mitral stenosis in the older age group and particularly in the female sex.

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PREMENSTRUAL TENSION

Its Relation to Abnormal Water Storage

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THE bleeding phase of the menstrual cycle rarely appears unannounced. Signs and symptoms that herald its approach are experienced by many women. Anxiety states, depression, lower-abdominal pain, lumbar pain, thirst, breast fullness and personality changes of a mildly antisocial nature announce the approaching condition. Menorrhalgia was suggested by Hamblen[1] as a descriptive term for this complex. These symptoms are accepted philosophically by most women, but there is a minority group, perhaps 25 per cent, who require medication. The syndrome has long been recognized. Hippocrates ascribed the symptoms to "agitated blood" seeking its channel of escape at the uterus. Police records of Paris from the early decades of this century show a striking increase in criminal acts of women during the premenstrual week.

There can be little doubt that the symptoms of premenstrual tension are related to abnormal water metabolism. In 1933 Thomas[2] reported 2 cases of unusual edema recurring cyclically during the premenstrual period. Associated with the edema were severe headache, abdominal fullness, leg pains and psychic changes that are now recognized as being related to premenstrual tension. Thomas observed that these symptoms disappeared coincidentally with the diuresis that occurs at the time of menstruation. Greenhill and Freed[3] called attention to its frequency and suggested treatment based on the abnormal water retention.

The etiology is unknown. That the disturbed water metabolism is related to ovarian steroid secretion seems probable. That some alteration in posterior-pituitary or adrenal-gland function induced by the cyclic production of ovarian steroids may be a factor is also possible. It should be recalled that water storage during the premenstrual period is normal; only when tissue hydration is excessive does the clinical syndrome of premenstrual tension appear.

The syndrome can be reproduced in part during the corpus-luteum phase of the cycle by the daily administration of pitressin, the water-fixing substance of the posterior pituitary. Water storage up to 4 lb. may be artificially induced in some patients and many of the symptoms likewise induced. However, it is not known whether or not there is increased pitressin secretion during the premenstrual period. Adrenal corticoids are increased premenstrually, and the edema following cortisone administration is associated with similar complaints. These observations provide interesting avenues for speculation about the etiology.

Clinical Study

A study has been made of a group of 22 patients between the ages of twenty-five and thirty-five years who complained of distress during the premenstrual epoch that was relieved at or near the onset of flow. Headaches, nervous irritability, insomnia, abdominal distention, low-back pain, pelvic fullness, breast tenderness and unusual thirst were the symptoms reported in order of frequency. The symptoms began in most patients about eight days prior to menstruation, but in others the duration of symptoms was shorter. The average duration of symptoms prior to menstruation was 6.9 days. In all patients the symptoms reached a crescendo just before or during the first few hours of menstruation, to be relieved at or near the onset of the flow.

Eighteen of the patients menstruated on a cycle of twenty-five to thirty-five days. The premenstrual tension syndrome was not observed in a cycle of less than twenty-five days. None of the patients complained of severe dysmenorrhea. Although the

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syndrome of premenstrual tension and dysmenorrhea may appear concurrently, it is the exception and not the rule.

Basal-temperature charts were kept on 16 of these patients and in each case showed a marked biphasic shift. The basal temperature often rose to 98.4°F. in the morning during the premenstrual week. Endometrial biopsies were taken on 12 patients at or near the onset of menstruation. A well developed secretory phase was found in each case. It appears that symptoms of premenstrual tension occur only in those patients who ovulate and who have active corpus-luteum function.

Treatment

Dehydration by Ammonium Chloride and Salt Restriction

Greenhill and Freed[3] have recommended dehydration during the premenstrual period by means of a salt-restricted diet and the administration of ammonium chloride in a dose of 1 gm. 4 times daily. In the group of 22 patients under study this treatment was administered to 16. Some found it difficult to tolerate the large doses of ammonium chloride, even when the drug was administered in enteric coating. The 16 patients had an average weight gain before treatment of 5.2 lb. — a group whose condition could be classified as severe. Treatment was instituted five to eight days before expected menstruation and maintained daily until onset of flow. Strict adherence to this regime produced only partial relief of symptoms in these patients. The average weight gain for the treated group was 4.3 lb. Most of the patients thought that the partial relief obtained was insufficient to justify repeated treatment in subsequent months. All of them complained about the salt-restricted diet, and the majority complained of gastric irritation from the large doses of ammonium chloride.

Dehydration with Pyrilamine 8 Bromo Theophyllinate

In this group of 22 patients with severe premenstrual tension dehydration with a new drug, pyrilamine 8 bromo theophyllinate, was attempted. The majority of patients were partially or totally incapacitated during the premenstrual week. Five of them were bedridden for 1 to 3 days before menstruation. The 22 cases under consideration were, so far as could be determined, patients whose sole complaint was premenstrual tension. Headache, breast pain, backache, nervous tension, abdominal pain and emotional instability were the major symptoms.

The 22 patients in the clinical study had previously received some form of treatment with more or less disappointment. Sixteen of them had been treated with ammonium chloride and salt restriction with only partial relief. They were observed for a minimum of one to two months without treatment, during which time weight was recorded at weekly intervals. Without treatment the average weight gain for the group during the premenstrual week was 6.8 lb.; the largest individual gain was 11.5 lb. and the smallest was 4.2 lb. An attempt was made to record the intake and output of fluid during these cycles, but the inevitable error arising from the patient's failure to note accurately her fluid intake and output makes the results of doubtful value. On the basis of the patients' own records, the average urine output in the first twenty-four hours of menstruation was 3270 cc.

The patients were given tablets of pyrilamine 8 bromo theophyllinate, 50 mg. to each tablet, and instructed to take 1 of these tablets 3 times a day beginning 10 days before menstruation. Medication was stopped at the first sign of menstruation. The average weight gain for the group of 22 patients after treatment was 1.4 lb. Thirteen of the patients were studied in the succeeding cycle with the same treatment, and the average weight gain was found to be 1.6 lb. Eight patients in the series agreed to record their weights during a third cycle without treatment. The average weight gain for this group in the untreated cycle was 6.9 lb. Although the patients' own records on urine output may not be reliable, the 22 patients reported an average output of 1450 cc. during the twenty-four hours of menstruation following the treated cycles. This stands in contrast to the 3270 cc. that the same group reported during a control cycle in which no treatment was given. Symptomatic relief closely paralleled the lesser weight gain during the treated cycles.

The drug effects no permanent alteration of water metabolism, and clinical relief is obtained only during the period of treatment. In some patients who are not included in this series, treatment was instituted after the symptoms of premenstrual tension had developed. A diuresis of some degree invariably followed in these patients, and most of them were relieved in part or in whole of their premenstrual symptoms.

Study of Water and Chloride Metabolism in Rats

When rats were fed measured amounts of water and placed in a metabolism cage it was possible to recover 104 per cent of the administered water during a four-hour collection period, water itself being something of a diuretic. When pitressin in a dose of 0.5 unit per rat was administered subcutaneously to the animals only 37 per cent of the administered water was recovered in four hours. To measure the diuretic effect of a drug to be employed in premenstrual tension, water storage may be satisfactorily induced in an animal by the administration of pitressin, employing a modification of the technic described in the *British Pharmacoporia*.[4] When pyrilamine 8 bromo theophyllinate in a dose of 0.1 gm. per kg. is administered orally to the rat with 5 cc. of water per 100 gm. of body

weight and pitressin in a dose of 0.5 unit (subcutaneously) the antidiuretic effect of the pitressin is neutralized, as is shown by a recovery of 92 per cent of the administered water in the four hours. When the experiments on rats were repeated, using ammonium chloride in a dose of 0.1 gm. per kg. instead of the pyrilamine 8 bromo theophyllinate, only 34 per cent of the administered water was recovered in four hours.

Water in the same volume, 5 cc. per 100 gm. of body weight, was given to a group of rats that also received pitressin subcutaneously and testosterone intramuscularly. The hormone was administered as testosterone propionate in a dose of 5 mg. given intramuscularly at 4 p.m. on the day preceding the test and repeated at test time on the following day. Water recovery in this group of animals was 23 per cent.

Chloride excretion, as measured by the Volhard–Arnold method, was studied in each group of animals along with the quantitative determination of water recovery. Those animals who received water alone excreted an average of 24 mg. of total chlorides per cage of 4 rats in four hours. The animals that received water and pitressin excreted 68 mg., whereas those to which water, pitressin and ammonium chloride were given excreted 82 mg. (figure uncorrected for chloride administered). The cages containing 4 rats treated with water, pitressin and testosterone yielded an average of 52 mg. of total chlorides. The cages containing rats that received water, pitressin and pyrilamine 8 bromo theophyllinate yielded an average of 102 mg. (Table 1).

Table 1. *Excretion of Water and Chlorides in the Male Rat.**

Dose	Average Percentage of Water Recovery	Average Total Chlorides per Cage of 4 Rats
		mg.
Water	104	24
Water, testosterone	112	28
Water, ammonium chloride (0.1 gm. per kg.)	91	—
Water, pyrilamine 8 bromo theophyllinate	136	68
Water, pitressin	37	68
Water, pitressin, testosterone	23	52
Water, pitressin, ammonium chloride (0.1 gm. per kg.)	32	82
Water, pitressin, ammonium chloride (0.5 gm. per kg.)	75	73
Water, pitressin, pyrilamine 8 bromo theophyllinate	92	102

*Test period = 4 hours.
Water = 5 cc. per 100 gm. per body weight (orally).
Pitressin = 0.5 unit per rat (subcutaneously).
Testosterone propionate = 5 mg. at 4 p.m. on day preceding test, and again at test time (intramuscularly).
Ammonium chloride = 0.5 mg. per kg. or 0.1 gm. per kg. (orally).
Pyrilamine 8 bromo theophyllinate = 0.1 gm. per kg. (orally).

Study of Water and Chloride Metabolism in the Human Female

Three hospitalized women volunteered to cooperate in a study of water and chloride metabolism. These patients were aged twenty-two, twenty-seven and thirty-two respectively. They were patients who had been subjected to no surgical trauma and who had no serious medical or surgical illness. They received no food or water after 9 p.m. On the following morning each patient was given 1000 cc. of tap water orally over a period of thirty minutes. At the same time each patient received 10 units of aqueous pitressin subcutaneously. The bladder was emptied by catheterization before the water was given and the catheter left in place and connected with a bedside bottle. The urine was collected over a period of four hours. During this period the patients excreted 106 cc., 275 cc. and 210 cc. respectively. The 3 patients were then allowed a regular diet until the evening, and at 9 p.m. all food and fluids were withheld. On the next morning each of the 3 patients received 1000 cc. of tap water orally and 10 units of aqueous pitressin subcutaneously. In addition, each was given pyrilamine 8 bromo theophyllinate in a dose of 100 mg. orally during the period of water ingestion. The dose was repeated two hours later and urine was collected from an indwelling catheter over a four-hour period. The urine excreted was 950 cc., 980 cc. and 1200 cc. respectively for each of the 3 patients. It is apparent from these figures that pyrilamine 8 bromo theophyllinate was able to neutralize almost completely the water-storage effect of pitressin (Table 2).

Table 2. *Water Excretion in the Human Female.**

Total Water Recovered After Administration of Water and Pitressin	
Patient 1	106 cc.
Patient 2	275 cc.
Patient 3	210 cc.
Total Water Recovered After Administration of Water, Pitressin and Pyrilamine 8 Bromo Theophyllinate	
Patient 1	950 cc.
Patient 2	980 cc.
Patient 3	1200 cc.

*Test period = 4 hours.
Water = 1000 cc. per patient.
Pitressin = 10 units per patient (subcutaneously).
Pyrilamine 8 bromo theophyllinate = 100 mg. at 8:15 a.m. on day of test, 100 mg. again at 10:15 a.m., orally.

Conclusions

Premenstrual tension is a symptom complex related to abnormal water storage during the premenstrual period. It is essentially a water toxemia. Intensity of symptoms varies with the amount of water retained. Symptoms are severe when premenstrual weight gain exceeds 5 lb.

The etiology of the disturbed water metabolism is unknown but appears to be related to some ovarian–pituitary–adrenal-gland complex.

In a study group of 22 patients with severe symptoms the average weight gain was 6.8 lb. This ab-

normal water storage was effectively blocked by pyrilamine 8 bromo theophyllinate but not by ammonium chloride. In 3 human females pitressin-induced edema was blocked by the compound.

Pitressin-induced edema in rats could not be unblocked by testosterone or ammonium chloride but was effectively unblocked by the new compound.

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MEDICAL PROGRESS

BLOOD GROUPING, BLOOD BANKING AND BLOOD TRANSFUSION (Concluded)*

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COLLECTION OF BLOOD

Blood collection, adequate in amount to cover the needs in all blood groups, is the major problem of all blood banks, large or small. This problem has three main aspects: those of the hospital, the community and the nation at large.

The problem of the hospital is one that existed long before the advent of banks, when the collection of blood was on an individual basis. Banks have eased the problem by creating an excess of donors for one patient whose blood could be used to care for the needs of others. Such a system, theoretically, should be effective, but, unfortunately, as blood has become available the demand for it has increased. Coupled with this has been the splitting of four blood groups into eight by the Rh factor. For certain sensitized patients further subdivisions of the Rh factor must be taken into account, as well as the new blood types and subgroups that have been brought to light. To compensate, the blood bankers have sought methods of procurement that would ensure the availability of an adequate amount of blood. These methods have had two main points of pressure, — on the attending physicians and on the patients. In public wards in private hospitals, little or no pressure can be brought to bear on the patient by charging him for transfusions that he has failed to replace. He knows full well that most of his bill, if not all, will be forgiven at the end of his stay. The same situation prevails to a greater degree in the public hospitals giving entirely free care. Blood used for such patients without prior donation is often not replaced. Pressure applied on the doctors by means of a debit-credit system applied individually or to a service is usually necessary for obtaining blood. The former, used in some public hospitals, attaches to each member of a house staff a debit-credit system whereby he is limited in the transfusions he may order by his standing in the bank. The latter applies an equal pressure to a ward or a service. Neither of these systems interferes with emergency transfusions, but both promote a lively interest among house officers in keeping up their credits to avoid interference with their surgery or medical therapy.

The second point of pressure, that directly on the patient, is usually exerted through his family. In public hospitals this pressure is exerted by direct contact between the doctor and the patient or his family or by organized groups who are interested in the hospital and who recruit donors among relatives and friends of the patients. These methods, whether they comprise threat or cajolery, are not nearly so effective after transfusion as before. What can be done by a group of volunteers working in a public hospital has been well shown by the Woman's Auxiliary of the Boston City Hospital, whose members contact friends and relatives of patients at the visitors' desk each day and lead them to the bank. Their efforts have brought about a considerable increase in the amount of blood available in the bank. In private hospitals, the pressure on ward patients is made greater by threatening them with a charge for blood replacement. Early contact of families is also important here. One method of achieving this has been by means of a voluntary or paid secretary. Through her hands go all the blood-grouping slips and blood requisitions. On the former slip space is provided for listing the number of transfusions that will be required. The secretary can then contact families by telephone or mail to bring in donors. If she sees the requisitions, she has an opportunity to know how much blood has actually been ordered. The introduction of this system at the Massachusetts General Hospital increased the excess of donations over transfusions dispensed from 1 per cent to 10 per cent in the first year of its adoption. For small

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blood banks the problem of having a sufficient excess of blood on hand to provide adequate coverage of the rare blood groups is often acute. To meet this the banks have sometimes organized panels of donors among civic groups from whom blood may be obtained in emergencies. Many such banks have resorted to a two-for-one or even a three-for-one system of blood replacement. For the patient requiring but one pint of blood this system works but little hardship, but for the person who receives a large number the burden is great. To ease this burden, some banks demand two-for-one for the first transfusion and one-for-one for those given subsequently. Another method has been to allow the donation of a second pint of blood to cancel the service charge for the grouping, cross-matching and administration of blood. If the service charge is in excess of cost and the hospital has access to professional donors, this method not only permits supplementing an insufficient supply of blood on hand but permits the blood to be purchased in the groups in which it is needed, — or as fresh blood when required.

The maturing process of blood banks has included the realization that they form but a part of a system of banks serving the patients in an area. By pooling of resources in a community, the excesses and deficits of blood in the different groups in individual banks can often be leveled to avoid enforcing systems of blood procurement that work hardships on patients or doctors. There have been and still exist two major obstacles to blood exchange. The first is a lack of standardization of bleeding bottles and equipment on the part of the commercial companies that supply them. The second is the lack of uniform methods of blood-bank control on a state or national level to ensure that the blood distributed by one bank has been drawn with the same degree of safety as that distributed by the next. Progress is being made in solving these problems, but only a concerted, organized effort on the part of blood-bankers themselves will ensure a final solution to them. In some areas, standardization has been achieved by the establishment of community blood banks. These have been under the auspices, if not the direction, of local medical societies and have been very effective. Under these systems, one bank supplies the hospital needs in the area in return for service charges and the hospital's supplying the donors. If the hospitals under such systems keep blood on hand for emergencies so that there is no delay in obtaining it, their patients derive great benefit from being served by large banks that can cover all the blood groups and provide uniform service. Outstanding examples of how such services can work are provided by the Alameda County Blood Bank in California, the King County Blood Bank in Washington and the Dade County Bank in Florida.

Blood collection by a single national agency has not been attempted, nor is it yet really visualized as a possibility. The need of blood for the armed forces and the necessity of an organization capable of procuring the vast amounts of blood that would be required to provide adequate care for the victims of wide-scale atomic bombings in this country now make such an organization necessary. The development of the Red Cross Blood Program is the nearest approach so far to the solution of this problem. To most practicing physicians it seems preferable to a governmental program and more likely to succeed. A union of private blood banks, under medical-society auspices, has been thought of as an alternative, but as yet no practical plan has been forthcoming for such an organization. The Red Cross Program, operating exclusively for the collection of whole blood and plasma for use by the armed forces, was extremely successful in the last war. On the basis of this success it was reorganized three years ago to provide blood for civilian hospitals and to develop a more widespread system for blood collection in the interests of defense and a means of providing plasma and plasma fractions. Aside from the mechanical difficulties of setting up such a program, the Red Cross ran into considerable opposition from those members of the public who were not disposed toward it and from some elements of the medical profession, mainly blood bankers, who thought that it would encroach on their prerogatives as well as their sources of income. Aided tremendously by the impetus given it by the Korean War, the Red Cross now has some forty blood-collecting centers, with more in prospect. It is currently collecting blood at a rate estimated to exceed two million pints a year. The Red Cross has been appointed by the government as the official collecting agency for the armed forces. It has been able, to date, with assistance from some large blood banks, to supply all the blood demanded for use by the armed forces. In addition, it must provide a new stock of irradiated plasma for the Armed Forces in very large amounts. In New England it has three programs, — one for Vermont and Northern New Hampshire, one for Connecticut and one for Massachusetts. The first of these is meeting total civilian blood needs; the other two are supplying about three quarters of the civilian hospital demand. All three are supplying whole blood and plasma for the armed forces. There is as yet no Red Cross Program for supplying plasma for civil-defense stockpiles, nor is there any prospect of one for some months, despite present hopelessly inadequate supplies of plasma. The function of the Red Cross as a national blood-procurement agency has not crystallized in a definite form. Originally its aim was to supply total hospital needs in each area served. This program led to the closing of many useful hospital banks, with a depreciation of pa-

tient-transfusion service in some areas when the supply became short. Departures from this original service have led to supplemental programs in some areas, hospital collection as deputy Red Cross banks in others and the setting up of credit-debit systems in still other sections of the country. In some cities and counties the opposition to the program as a whole is still so great that the local medical societies have refused to let the Red Cross set up banks. From this confusion certain concepts are gradually emerging. The first of these is that the Red Cross can make good collections and give good service in most small and medium-sized towns, where there is good organization of their local Red Cross Chapters and a strong community spirit. Donor recruitment by the local chapters is the kernel of the nut; where it is good, the blood supply will be adequate. The second concept is that most large urban areas are difficult places in which to collect blood for a civilian program, though good for a war program. The third concept has been the recognition by blood bankers, the medical profession and the Red Cross that hospital and other banks are, with rare exceptions, necessary blood-collecting agencies. Donors will give for friends, relatives, civilian and veterans' groups and hospitals, sometimes, when they will not give blood for the Red Cross. The abandonment of banks at which the blood of these persons may be collected represents a foolish loss of a useful source of transfusions. For civil defense, phlebotomists, bleeding equipment and storage space will be vitally necessary. To dispense with banks that possess these faculties is shortsighted. Many patients would rather pay for the blood they receive than seek donors. Consequently, they provide money to pay professional donors, who are usually penurious. These professionals can only be dealt with by private blood banks. In Massachusetts at present, about 4 per cent of the blood used comes from professionals, a useful source of supply. The fourth concept is that the control exerted by the medical societies over the Red Cross Blood Program is one of the most important factors in making it serve the needs of the hospitals. Where the medical societies have set up active, interested committees for supervision of the Red Cross Program (without which it cannot function, according to its own rules), the system has worked well for patients, physicians and banks alike. No two communities face the same transfusion problems. For each the solutions lie in the intelligent supervision of blood collection and distribution by the physicians. This system works at its best when the blood bankers have a large share in controlling the workings of their local program. The fact that no charge for blood is permissible under the Red Cross program does not mean a loss of revenue to hospitals or banks, as they are allowed to charge for laboratory work and administration of the blood. Furthermore, many hospitals, by permitting blood donations to replace the service charges, were enabled to abandon their previous two-for-one systems when the Red Cross began to supply blood. The Red Cross blood program is not yet in its final form. Many problems are still to be solved in its management, but it has already achieved a major portion of its goal. It has helped thousands of impoverished and kinless patients. With proper supervision by blood bankers it should be no threat to private enterprise but a valuable adjunct to patient care. For the nation as a whole it is the best solution found to date for the problem of supplying blood for the armed forces and for defense.

The Handling of the Blood Donor

The screening of donors in order to ensure that their blood will transmit no diseases to recipients has slowly improved in the past twenty years, but as yet no universal agreement exists concerning exactly what diseases are harmful. Coupled with this problem is the care of the blood donor. Banks have done much to stimulate an interest in him as an individual and to formulate the philosophy that the giving of blood should not be the act by which a well person becomes sick. These two problems are best regarded as one, under the heading of "the handling of the blood donor." The initial contact with the donor is important. At the first interview the bank can save him and itself trouble by outlining the diseases that prohibit donation and by then giving him an appointment, which will save him time. Care must be taken in establishing the identity of each donor on arrival at a bank, by name, number, age and address. The initial screening process is often left to secretaries, technicians or volunteers. Unless this survey is confirmed by a nurse, or preferably by a doctor, a history of important transmissible diseases may be missed. After this, the donor is made ready for phlebotomy and proceeds to the bleeding room. His blood is taken; he rests for an adequate period, is fed, and then, unless he feels faint or has other untoward symptoms, leaves. In actual practice this simple routine can be amplified to advantage. The use of volunteers to guide the donors, to assist them with their clothing and above all to make them feel that their donation is appreciated and that they are being accorded personal attention is an important part of their care. The availability of a physician who is familiar with postphlebotomy reactions is necessary.

Although it is impossible to lay down hard-and-fast rules about the handling of donors, the results of the accumulated experience with some 45,000 as gathered by Yatsuhashi and Grove-Rasmussen at the Massachusetts General Hospital are helpful in throwing some light on the subject.[93] All donors in their series had histories of diseases checked off by volunteers, temperatures and hemoglobin de-

terminations noted by technicians and a final history and a limited physical examination performed by an intern. The percentage of donors rejected ranged from 14.5 per cent before prospective ones were given instruction ahead of time about what disease states would cause rejection to 7.7 per cent after this system was adopted, with an average of 9.0 per cent. A low hemoglobin (below 85 per cent, or 13 gm.) was the chief cause for rejection. The number rejected for this cause varied from year to year but was, on an average, about 40 per cent of all causes. The hemoglobin level was determined by the specific-gravity method, using cupric sulfate. Because of the findings of Barer and Fowler[96] that a number of persons (25.8 per cent in the series) failed to regenerate their blood completely in two months after donation, a baseline was established for each of our professional donors by a photohemoglobin determination made prior to the first donation. A return to within 0.2 gm. of this level was established as necessary prior to subsequent donations in the hope of avoiding the occurrence of aplastic anemia among these persons. No donors were recalled until two months had elapsed after donation. Because of a wide variance of time intervals between bleedings among these professionals, no accurate statistics have been collected on their ability to regenerate their blood to prephlebotomy levels. No case of aplastic anemia has been reported, however, after over 10,000 transfusions given by these persons. About 14 per cent of the donors who were rejected were refused on a basis of an elevated systolic blood pressure (over 180) or a diastolic pressure of over 110. Too low a blood pressure (systolic of 100 or less) caused the rejection of 2 per cent. Although high blood pressure cannot be considered *per se* as a contraindication to phlebotomy, isolated instances of syncope and prolonged hypotension did occur after bleeding of donors with pressures above these levels before these rules were introduced. Should hypertensive subjects require therapeutic phlebotomies, these can be performed by a physician in an emergency ward, where adequate rest and observation are available in the event of complications. We have no statistics concerning unfavorable response by hypotensive subjects to phlebotomy. Their rejection to date has been made on an arbitrary basis. Experience in other banks has not always paralleled our own, and in many banks blood-pressure determinations either are not done or are disregarded. The consensus among blood bankers, however, favors the more conservative measure of rejecting hypotensive and hypertensive subjects alike. Elevations of temperature of 99.6°F. or more accounted for 3 per cent of the rejections. These rejections were made on the grounds that the patient was succumbing to an infectious process, possibly transmissible, that might be made worse by phlebotomy. Upper-respiratory infections diagnosed by history, presence of nasal discharge or palpable cervical glands accounted for 5 per cent of the rejections.

Prior to 1947, donors were requested not to eat within four hours before phlebotomy. After this time no attempt was made to curtail eating for the following reasons: First, many ate regardless but lied about it; secondly, a number of fasting donors felt faint prior to donation and little better afterward despite being fed crackers and milk; thirdly, we had learned to disregard the unwholesome-appearing fat in the supernatant plasma of banked blood as harmless to the recipient, and lastly, the incidence of allergic reactions among recipients (about 0.7 per cent when fasting was in force) fell to 0.4 per cent after this restriction was abandoned, — a change of no statistical significance. The theoretical possibility remains, however, that patients with food allergies may have severe reactions to the blood of donors who have just eaten such foods. We have had two incidences of such reactions, both mild. Other blood bankers have also had similar experiences without serious consequences. The gist of the matter is that fasting upsets the donor, its benefits are not statistically obvious, it is difficult to enforce and the untoward results of eating prior to donation are not common or, in our experience, severe.

Debilitating diseases, too short an interval between phlebotomies, recent surgery, diabetes, pregnancy within six months and so forth were all used as reasons for rejection. Usually such prospective donors can be eliminated by proper instruction before they reach the bank. Diseases, transmissible by transfusion, are more obvious causes for donor rejection. Asthma and the allergies are the most controversial of these. Although there are examples of temporary transmission of sensitivity to ragweed pollen and other allergies to patients in our series and others, there is some reluctance among blood bankers to refuse to take blood from such persons at a time when pollens or other sources of sensitivity are not available to the potential recipient. It is perhaps wise to remember, however, that allergies are often multiple, although a prospective donor may believe he has only one. Hence, our caution in bleeding persons with a history of allergy may be justified. Syphilis is readily transmissible by transfusion of fresh blood, but the spirochete will die if stored at refrigerator temperatures for ninety-six hours.[97] Most cases of transmission of the disease by transfusion have occurred when the donor was in the incubation period or seronegative phase of the disease.[98] Manifestations of the disease, usually secondary lesions, will appear within a few weeks to five months after inoculation.[99] They are usually far more virulent in appearance than when the disease is acquired in the conventional manner.

Serologic tests, physical examinations and refrigeration for ninety-six hours will eliminate the dangers of transfusion syphilis. Malaria is readily transmissible, as the plasmodium will live under all conditions in which the red cell will survive, including refrigeration. The interval between donation and the occurrence of the original symptoms of the disease is of no significance. One donor in our series transmitted the disease twenty-five years after noting his last known symptom. The use as donors of persons who have lived in areas where the disease was endemic but who have not contracted it is one of the new postwar problems. The consensus has been that it is probably wiser to reject these subjects, unless they were given suppressive therapy while in the area and have shown no symptoms for two years thereafter. Some thought must be given to the difference between a region like our own where the disease is rare (and hence the recipients are potentially vulnerable) and areas like those in some South American countries, where well over half the population has had malaria. In the latter, the elimination of donors on a basis of history of malaria would close the blood banks, and the danger to the recipients is not so great in this area. Infectious jaundice, brucellosis and similar blood-borne infections are transmissible; these caused a small number of rejections in this series. Refrigeration does not affect the organisms involved. Although statistics concerning the incidence of homologous serum jaundice following transfusion of whole blood cannot be obtained from our series, 3 deaths from the disease are known to have occurred in the last 18,000 consecutive transfusions.

Physical examinations are made in some banks and not in others. We have regarded them as of value, and many donors have appreciated them as an evidence of the thoroughness of their care. Donors rejected because of them or for other causes were referred to their own physicians for care when necessary. Heart disease, not diagnosed but suspected on the basis of symptoms or because of pulse irregularities, murmurs, bradycardia (pulse rate of 60 or less) and tachycardia (pulse rate of 100 or over), accounted for 3 per cent of all who were rejected. One subject who was rejected for a heart murmur died unexpectedly two days later while shoveling snow. The liability of the bank, had he given blood, would have been difficult to establish. Enlarged lymph nodes, evidences of respiratory infections, skin disorders and penile lesions have accounted for about 5 per cent of our rejections. No attempt has been made to examine the genitalia of females. Discharge or lesions resembling chancres led to the rejection of 11 males. Three were proved to have syphilitic chancres. The incidence of serologically proved syphilis for 45,000 donors in the same period was 1.6 per cent.

Donors who have been drinking alcoholic beverages create problems for blood banks. In the first place, they are often difficult to handle. In the second, they are sometimes obnoxious to other donors. Thirdly, some of them, if bled, will show a marked fall in blood pressure, accompanied by syncope. The transmission of the alcohol to the recipient is probably of little harm.

An adequate rest period after phlebotomy is most important for the avoidance of syncope. This is best divided into a period when the donor lies down, and one in which he sits for a while. Fifteen to twenty minutes for the first and at least ten for the second will usually suffice. With this method, the known incidence for syncope among 45,000 donors in our series was 0.1 per cent.

In summary, in our own experience and in that of others, care should be taken by blood banks to select donors whose blood will not transmit diseases to patients and for whom donation will not be harmful. Great care should be taken in handling the donor, both physically and mentally. He should be carefully observed after phlebotomy to ascertain that he has suffered no ill effects. His treatment by the personnel of the blood bank should be courteous and thorough, so that he will feel that he has had the best of care.

Technics of Phlebotomy

Phlebotomy, as it is customarily performed, involves the penetration of one of the basilic or cephalic veins in the antecubital region with a needle that communicates, via a 12- to 24-inch length of tubing, with a 550- to 700-ml. bottle containing an anticoagulant-preservative blood diluent, ACD (acid-dextrose-citrate) solution. In preparation for venesection, a rubber tourniquet or a pneumatic sphygmomanometer cuff is applied to one of the donor's arms. The antecubital area is then cleansed with a detergent and sterilized by the application of an effective bactericidal agent. Next, the skin at the point of needle entry is anesthetized by the intracutaneous injection of procaine, administered with needles and syringes that have been sterilized by autoclaving since last used. This precaution should be considered obligatory from the standpoint of preventing the dissemination of hepatitis in donor clinics, the risk of viral transmission when multiple inoculations are supplied from a common syringe having been well established.[100]

The vein selected for phlebotomy having been distended by constriction of the tourniquet (or by inflation of the cuff to a pressure between 50 and 80 mm.), it is immobilized by the pressure and traction of the phlebotomist's thumb. The phlebotomy needle is now introduced into the procaine bleb, entering the skin at a point approximately ¼ to ½ inch proximal to the point of expected contact with the vein. Having penetrated the vessel,

it is projected, with tip elevated, into the lumen for a distance of at least ¼-½ inch. Blood should commence to flow immediately and continue to flow without interruption until 450 to 500 ml. has accumulated in the set.

With adequate collection apparatus, access to a suitable vein and observance of a few simple principles, some of which are listed below, complete collection can usually be anticipated within six to ten minutes. Technical considerations that deserve particular stress include the following:

The venesection needle, the quality of which frequently determines the success or failure of phlebotomy, should be of 14- to 16-gauge caliber, prepared with a concave bevel of medium length and tipped with a very sharp, barb-free point.

As a basis for selection, the location of a vein and the stability of its anchorage in the tissues are more important than its apparent caliber. Superficial veins that are tortuous, thick-walled and easily "rolled" should be avoided.

If the vein of choice is very superficial in its location, it should be entered from its lateral rather than its superficial aspect, for if the channel communicating between the lumen and the external skin surface is too short there may be leakage of blood around the needle.

The difficulties of venipuncture are increased if an excessive volume of procaine is deposited in close proximity to the vein. A small quantity introduced intracutaneously and an equally small deposit immediately adjacent to the vein will provide effective anesthesia. Rapid injections of procaine can be more painful than venesections without anesthesia; performed deliberately, they are less painful.

Premature interruption of venous flow during phlebotomy is often due to an undetected loosening of the tourniquet or deflation of the cuff. If venostasis is applied immediately the situation can be corrected and flow re-established. Another common source of difficulty is the close approximation of the needle aperture to the vein wall, which is corrected by rotating and withdrawing the needle slightly.

Tenderness and swelling in the neighborhood of the venipuncture, a sign that blood is escaping from a laceration of the vein, is the signal for immediate release of the tourniquet and removal of the needle from the arm. Venipunctures should not be performed near the site of recent hematoma formation and should never be attempted in the same arm until at least twenty minutes have elapsed after the injury.

The standard equipment for blood collection and transfusion is of two principal varieties, — the "vacuum set" and the "gravity set." The vacuum set employs a flask from which air has been evacuated. No air vent is required for the entrance of blood, and the flask is entered only once prior to the storage and injection of its contents. The gravity set depends on hydrostatic pressure for the filling as well as the emptying of the flask. Since its contents are always at atmospheric pressure, an outlet must be provided for the venting of air during venesection.

From the standpoint of bacterial contamination, the vacuum equipment is theoretically safer. Unless precautions are taken, however, bacterial invasion of the vacuum bottle can easily occur by virtue of the pressure gradient existing between the internal and external surface of the diaphragm closure, the effect of which is to facilitate the entrance of contaminants. Expert phlebotomy is more easily performed with a gravity set than with vacuum equipment, for unless the valve governing the flow rate is adjusted correctly donor blood will enter the flask in the form of a high-velocity spray or foam, causing hemolysis and the precipitation of fibrin clots. Hemolysis and clotting are also promoted by the presence of a glass airway tube in the bottle. In order to avoid these complications this flask should be filled in the inverted position at a rate not exceeding 50 to 75 ml. per minute, and its contents should be disturbed no more than is necessary to ensure adequate mixing of blood and diluent.

Various modifications in the design and construction of phlebotomy equipment are currently under investigation, the most radical and promising of which is the substitution of a collapsible plastic bag for the standard glass bottle.[101] Present models* are constructed of polyvinyl chloride acetate copolymer, a relatively heat-stable material that withstands autoclaving. Relatively small in bulk, light in weight and almost immune to breakage, sets of this type can be packaged, stored and transported with ease. A blood bag, in contrast to a blood bottle, requires no air vent, as no air is displaced during filling or emptying. Moreover, it can either be emptied by gravity drainage or evacuated by direct compression, as by the weight of the patient's own body or by an inflated sphygmomanometer cuff, so that blood may be injected rapidly under high, controlled pressure and without risk of air embolism.

The damaging effects of glass and air interfaces are eliminated in plastic bag sets. These protective features have also been extended to include the venesection needle, its stainless steel surface having been modified by the application of dicocodimethyl ammonium chloride† and other thermostable monomolecular coatings with nonwetting or platelet-repellent properties. Needles have been reshaped for laminar flow, that is, in a manner that prevents turbulence and eliminates air entrapments. Pre-

*Equipment of this type is now available commercially from Fenwall Laboratory, Incorporated, Ashland, Massachusetts.

†"Arquad 2C," distributed by Rohm and Haas Company, Philadelphia.

liminary observations[102] indicate that these modifications of needle design are of value in preventing premature clotting during the venesection. However, clotting caused by tissue activator is not inhibited as a result of these improvements, and its avoidance still depends on the successful performance of a nontraumatic venipuncture.

The Blood Bank in Relation to Therapy on the Wards

In some hospitals, in the past ten years, complete intravenous-therapy services have been established. These services usually embrace under a single head a solution room (if solutions are made instead of purchased), a blood bank and the attendance of nurses for intravenous therapy. The purpose of such combinations is to provide better integration of related types of therapy. The most important part of this innovation has been the employment of nurses for intravenous therapy. Placed under the direction of the head of the blood bank, they can, if properly trained and supervised, give blood and intravenous solutions with greater skill and safety than if such treatments were carried out individually by doctors. They quickly learn to recognize, care for and report transfusion reactions. It is easier to enforce among them than among doctors a period of observation of all transfusions for the first five minutes to ensure that a severe hemolytic reaction does not occur. They can, if orders are written in advance, administer fluids parenterally to patients early each day,—which is often difficult for doctors to do. They become more skilled in the use of needles than those who use them infrequently, which indicates less painful treatments for patients and fewer damaged veins. However, they usually cannot provide twenty-four-hour coverage of the wards unless a sufficient volume of work permits their employment. Moreover, the employment of nurses for the giving of infusions interferes with the training of interns in becoming adept with needles. A solution to this problem is to arrange for the interns to give all the infusions on the public wards. The temptation to have nurses give medicines intravenously is great, but care must be taken not to allow them to administer dangerous drugs that a physician should give in person.

The storage and the making of solutions for use on the wards are best handled in a central location, provided that an adequate method of distribution can be worked out. Three methods of distribution are currently in use. One is the haphazard method of requisitioning supplies when needed, a method that interrupts ward care, delays therapy and continually bothers the central supply room. The second is for the wards to return used equipment to the central supply room at a certain time each day in exchange for replacements and extra equipment as needed. This needlessly hampers both ward personnel and central supply personnel during part of the working hours. A better method is for the central supply room to send out supplies to the wards on a quota basis in the nonworking hours by means of a staff of low-salary transporters who bring back used equipment. This means uninterrupted work on the wards and in the central supply room as well as a constant supply of material on hand in adequate amounts.

For the blood banker, the control of these services is very helpful to the running of his bank. It means not only that blood collection, storage and processing are under his supervision but that its administration, along with that of other fluids, can be adequately supervised. Few blood bankers act in more than an advisory capacity to the clinical staff concerning when blood should be given patients or in what form, but, conversely, the blood banker cannot give good service to clinicians if he is unaware of their needs or of how the blood is being administered. Great care must be exercised to ensure that blood is available when needed and is distributed properly. In this regard, many banks have had to insist that blood be ordered well in advance of the time it is wanted (when possible) so that care might be taken in the performance of groupings, cross-matchings and all the clerical work attendant on these procedures. This avoids errors caused by haste. The hurried "setting up" of bloods in the late afternoon by a tired staff can readily cause errors. Another important step in providing safe transfusion care has been the encouraging of physicians to have transfusions "set up" and ready in case of need, particularly prior to operations, even though they may not expect to use them. This step has materially reduced hurried emergency work in the laboratory. It also has enabled banks to have blood on hand for transfusion when the patient's blood has been of a rare group and Rh type. Blood for grouping the patient should be obtained by the blood-bank staff whenever possible to avoid errors in labeling the test tubes. Increasing attention is now being given to the identification of transfusions prior to administration. The notation of the complete name of the patient and his hospital number, room number, and physician's name on the flask of blood help the person administering the blood to identify it clearly. The name and number of the donor should also be listed with the results of cross-matching. Clerical errors arising from inadequate identification are of increasing occurrence.

Three types of additional service rendered the clinician by the blood bank have become more common in the last ten years. The first is the use of the replacement transfusion. This is used most commonly in erythroblastosis of the newborn[8] but has a place in treating kidney failure, severe carbon-monoxide poisoning and, in certain instances, hemolytic transfusion reactions. It has been used,

but without much success, in severe leukemia. The second is the use of rapid transfusion by intravenous, intrasternal or intra-arterial routes. Rapid transfusions are most usually employed during radical operations to keep up with excessive blood loss. As stated under "Transfusion Reactions," the use of multiple transfusions through large-bore (15-gauge) needles with adequate gravity will usually keep up with severe hemorrhage.[91] Blood pumps and plastic bags compressed manually or by a blood-pressure cuff are safer means of obtaining rapid infusion than the use of air or oxygen under pressure. The intra-arterial route of transfusion is indicated when it becomes necessary to restore the systolic pressure rapidly without running the danger of overloading the right heart.[102] Complications of intra-arterial transfusion include arterial spasm and even gangrene of the limb; hence its routine use is rarely justified.[104] All pressure mechanisms cause increased cell destruction and hemolysis, which may damage the kidneys. The third form of therapy is the use of an autotransfusion set. Such a set, to be effective, must be of efficient design and constantly available. An ordinary blood-donor set is not very effective. At the Massachusetts General Hospital autotransfusion has been used at the rate of about 100 times a year for the past five years and somewhat less frequently prior to that. The apparatus employed consists of a quart jar with a two-hole stainless-steel cover. The openings in the tubing and cover are progressive in size from the suction tip to the bottle in order to prevent blockage by clot, the smallest opening being 4 mm. in diameter. This set must be kept sterile. When it is to be used it is attached by the scrub nurse to suction, and citrate solution is then drawn into it. Our experience has been similar to Griswold's,[105] in that no dire results have come from the contamination of fresh blood with small amounts of feces, bile, urine or ascitic fluid. The use of this apparatus in the presence of old clotted or hemolysed blood, frank infection or thrombin is contraindicated. It can be used for any severe intra-abdominal, intrathoracic or other fresh hemorrhage as a stopgap until banked or fresh blood is available. Tests made on the blood collected in this manner have demonstrated the following: In the first place, the blood continues to clot for a period of some minutes to an hour after collection. Hence, if it is allowed to stand after preliminary filtration it may need to be filtered again. In the second place, the degree of hemolysis in this blood is often severe. This may be caused by the high degree of negative pressure used in the operating room or by the phenomenon called "frothing," which results from violent mixing of air and blood. The latter is very harmful to the red cells. In a few measurements with a spectrophotometer, the degree of hemolysis in blood so collected was in the range of 400 to 600 mg. per 100 cc. The observable hemolysis in the supernatant serum in a large number of flasks of blood so collected was very obvious. Thus, the amount of free hemoglobin administered to the patient, although derived from his own cells, can approach dangerous levels, particularly when multiple transfusions are given. For this reason, it must be clearly stated that because of the severe hemolysis that usually accompanies the use of the autotransfusion set its use should be curtailed to those patients in whom hemorrhage endangers life and for whom no other source of blood is immediately available.

The blood bank, to be of maximum usefulness to the hospital, should provide complete service, including the administration of transfusions.

Conclusion

There have been so many additions to our knowledge of blood groups, blood typing and cross-matching technics, blood-banking procedures, plasma fractionation and therapeutic potentialities of the plasma fractions that a review of even the most recent advances involves nearly the entire field. The entire subject has been reviewed, therefore, with special emphasis on the most important of the recent advances. The safety of blood-transfusion therapy depends to a large extent on proper blood typing and cross-matching. Two important new blood-group systems have been reported, and considerable experience with them has indicated, even more strikingly than was previously realized, the importance of blood groups other than the ABO and Rh groups in the occurrence of hemolytic transfusion reactions. Improvements in technics have greatly increased the ability to avoid transfusion accidents. Better understanding of the mechanism of shock and of bleeding disorders and the increasing availability of potent plasma fractions now allow a more effective approach to treatment, and current research promises to provide still more and better therapeutic agents. Experiments with new and vastly improved equipment are nearly complete; the resulting developments will make the collection and administration of blood much easier and safer. Of great importance are the recruitment and handling of blood donors and the organization of blood-transfusion services, which have been discussed on the basis of nine years' experience in a large general hospital.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37381

PRESENTATION OF CASE

A seventy-four-year-old man was admitted to the hospital because of intermittent right-upper-quadrant pain.

Six days prior to admission, after a heavy meal, the patient developed severe aching right-upper-quadrant pain, which extended through to the back but did not radiate. It disappeared spontaneously after an hour but returned again after he ate a frankfurt. He then became nauseated and vomited. The vomitus was thought to consist largely of partly digested food and to contain no blood. He remained nauseated until the time of admission, but there was no further vomiting. The pain persisted, with intermittent periods of relief and without change in character. He was seen by his doctor on several occasions when the pain was most severe and was given injections that produced relief. His bowels moved daily; they were light yellow in color. The urine was "wine colored." He did not note the onset of jaundice. His general condition deteriorated steadily, until by the time of admission he was very weak and seriously ill.

The patient had had typhoid fever in early adult life, with an uneventful recovery. Thirty-six years prior to admission a laparotomy had been performed because of jaundice; a report from the hospital indicated that a mass had been found in the region of the gall bladder that was thought grossly to represent inoperable cancer. A palliative cholecystojejunostomy was performed. After this he recovered completely and apparently had no subsequent difficulty until the present illness. His alcohol intake was limited to a moderate amount before dinner.

Physical examination showed a seriously ill, moderately jaundiced man. There was auricular fibrillation with a rate of 120 to 130; no murmurs were heard. Rales were present over the lower third of the left chest posteriorly. The abdomen was soft, with no palpable masses. The liver and spleen were not enlarged. There was tenderness and spasm to deep palpation in the right upper quadrant.

The temperature was 102°F., the pulse 120 and the respirations 28. The blood pressure was 108 systolic, 66 diastolic.

Urinalysis showed a specific gravity of 1.018, a ++ test for albumin, no sugar and occasional granular casts but no cells in the sediment. Examination of the blood revealed a hemoglobin of 14.8 gm. and a white-cell count of 18,400. The alkaline phosphatase was 8.7 units, the nonprotein nitrogen 61 mg., the blood sugar 120 mg., the serum amylase 22 mg. and the bilirubin 15.5 mg. direct, 17.4 mg. total per 100 cc.; the chloride was 99 milliequiv. per liter. The prothrombin time was 34 seconds (normal, 17 seconds). An electrocardiogram showed auricular fibrillation at 140 and nonspecific ST-segment and T-wave abnormalities.

After admission the patient's condition rapidly became worse. By the second hospital day the temperature had risen to 105°F. after a chill, and he was unresponsive. The abdomen became distended, and a Levine tube was inserted, which drained coffee-ground fluid by gravity. He was started on penicillin and streptomycin and was digitalized. Intravenously administered fluids and other supportive measures were given. A blood culture taken on the second hospital day grew *E. coli* in each of two flasks. Portable x-ray films of the chest showed no significant abnormalities. The abdominal roentgen studies, though somewhat unsatisfactory, demonstrated dilated loops of small bowel in the abdomen but no calculi in the region of the gall bladder and no air in the biliary tree. On the third day he was still critically ill but had shown some improvement. The temperature was down to 101°F. and the respirations and pulse were slower. However, he was more icteric and had a queer bronze

color. The stools were still clay colored. There was distention in the upper abdomen and some muscle spasm in the right upper quadrant. A urine test for urobilinogen showed 0.1 Ehrlich units.

A stool guaiac test made on the fifth day was ++++. The white-cell count was 16,400. The cephalin-flocculation test was ++++ in 48 hours. The nonprotein nitrogen was 176 mg., the serum albumin 2.4 gm. and the globulin 2.04 gm. per 100 cc. By the sixth day he was more responsive but still too ill to be moved for more definitive roentgen studies. The temperature ranged between 99 and 101°F. The prothrombin time had fallen to 23 seconds (normal, 17 seconds). The hemoglobin was 12.8 gm., the alkaline phosphatase 6.4 units, the nonprotein nitrogen 116 mg. and the serum bilirubin 14.5 mg. direct, 27.1 mg. total per 100 cc. An abdominal examination showed increasing right-upper-quadrant tenderness with some muscle spasm, although peristalsis was still present.

On the tenth day the patient had a severe nosebleed, and it was noted that he was developing ascites. The right-upper-quadrant pain and tenderness persisted, and he was passing tarry stools, but on the next day he passed a brown guaiac-negative stool. On the twelfth day, although he was still seriously ill, he was somewhat more alert and appeared less jaundiced. The nonprotein nitrogen was 84 mg. and the bilirubin 3.6 mg. direct, 5.0 mg. total per 100 cc.; the sodium was 148.6 milliequiv., the potassium 5.1 milliequiv. and the carbon dioxide 36.8 milliequiv. per liter. The feces were still brown. By the fifteenth day he appeared much improved. The abdomen was soft and the patient was alert. However, he had developed a troublesome herpetic lesion on the lip and had slight diarrhea. On the sixteenth day he was again in a state of mental confusion, though otherwise unchanged. He became unresponsive. The temperature had risen to 102°F., and there was dullness over the right lung base. The cephalin-flocculation test was ++ in 48 hours; the nonprotein nitrogen was 88 mg. and the bilirubin 1.4 mg. direct and 2.1 mg. total per 100 cc.

On the nineteenth day, antibiotic therapy, which had been discontinued during the period of improvement, was reinstituted. An x-ray film of the chest obtained in the supine position showed clear peripheral lung fields and normal position of the diaphragms. The white-cell count was 15,300 and the nonprotein nitrogen 122 mg. per 100 cc. The urine was still essentially negative. The patient continued to be unresponsive but had no localizing neurologic signs. Cheyne–Stokes respirations became more prominent, and he died on the twenty-sixth hospital day.

Differential Diagnosis

Dr. Allen G. Brailey*: When a patient comes into the hospital seriously ill and dies after a few days, there is likely to be very little historical information.

In arriving at the cause of this man's death I am required first to decide the cause of the jaundice. There is no reason to consider hemolysis as a reason for jaundice here, but did he have primarily hepatocellular disease or biliary obstruction? As is so often the case when this differentiation must be considered, the evidence is not clear cut or free from contradictions. In favor of obstruction may be mentioned these facts: He had typhoid fever in youth — a disease that is prone to involve the gall bladder and to initiate changes favorable to the formation of stones. Then at the age of thirty-eight years he had an illness characterized by jaundice for which he underwent operation. The mass that at the time was thought to be inoperable cancer must have been inflammatory in nature and probably involved the gall bladder. The final illness came on abruptly rather than insidiously and was characterized from the start by pain. The stools were described as yellow and later as clay colored. The urine was said to contain no bile, but it was described as wine colored — a poor term; one can only guess that the historian had in mind a red and not a white wine. A dark-colored urine may have resulted from concentration; it may have been due to blood or perhaps to bile. Urobilinogen in the urine was markedly diminished. At the end of three weeks he was very much better; the stools became brown and guaiac negative; the bilirubinemia diminished. These facts all suggest the likelihood of acute obstruction of the common duct with the subsequent release of obstruction and subsidence of symptoms.

On the other hand, although it is by no means unheard of, it is certainly somewhat unusual for a person who has had acute cholecystitis once to survive thirty-six years without a symptom. The cephalin-flocculation test was ++++ in 48 hours — a test that by itself is slightly more indicative of cellular damage than of obstruction. However, the test is never definitive, and this test seems to have been made after the patient had been severely ill for eleven days and might well have sustained a good deal of cellular damage secondary to obstruction.

I think he had biliary obstruction in spite of these minor objections. The next question is: What caused the obstruction? I know of no way to exclude carcinoma of the head of the pancreas, of the ampulla or of the gall bladder. It is true that he passed blood in his stools for a time. He may have had an unsuspected ulcer, but a stone in the common duct not infrequently results in bleeding. The abrupt and painful onset of the illness and the considerable relief of the obstruction, at least for a time, argue against cancer, and I think that I prefer the diagnosis of obstruction due to stone in the common duct or in the ampulla. I assume that the cholecystojejunostomy performed thirty-six

*Assistant physician, Massachusetts General Hospital.

years before admission was not maintained but that the normal biliary channel probably had become re-established.

However, it is obvious that other conditions were present as well. The fever, chills and leukocytosis can hardly be explained on any other ground than infection, and, in fact, a blood culture was positive for *E. coli*. Probably all obstructive jaundice has some accompanying cholangitis, and perhaps this infection was a fairly virulent involvement of the whole biliary tree. Or he may have had an empyema of the gall bladder. Either of these conditions may well have accounted for the tenderness and muscle spasm of the right upper quadrant that was reported. The infection was apparently controlled with antibiotics until the sixteenth hospital day, when the temperature again rose; the patient became unresponsive and rapidly went downhill to death. Perhaps this fatal outcome might have been prevented if antibiotics had been continued longer, or perhaps he developed a new complication such as a metastatic brain abscess or empyema elsewhere.

When I first read this protocol, I wondered if, initially, he did not have a pancreatitis as well. Certainly the manner of onset was very suggestive. Apparently the physicians caring for him thought so too, as a serum-amylase determination was made. It was normal. However, the test was made six days after the onset. If he did have pancreatitis as well as biliary obstruction, he may have had areas of fat necrosis that provided sites for subsequent abscess formation.

I assume that he had arteriosclerotic heart disease and that the renal failure was secondary to sepsis and circulatory embarrassment in a sick, old man. I believe he had biliary obstruction, probably due to a stone, that he had sepsis of the gall bladder or liver and that he may have had pancreatitis.

Dr. Daniel S. Ellis: This patient was admitted on the Surgical Service, but because his condition deteriorated so rapidly in the first twenty-four hours there was no possibility of operation. Our first impressions when he came in were similar to those outlined by Dr. Brailey. We had definite information that he had had a cholecystenterostomy, and there was no reason to suspect that it was not still open after it had been working for thirty-six years. It was hard to explain why, if it had worked and was still working, he had obstruction in the common duct and a pancreatitis. As the illness developed in the second twenty-four hours, it was obvious that infection was the primary difficulty. The temperature came down immediately on the institution of antibiotics, and on the basis of his chart he seemed to be getting well. However, his actual appearance was quite different. For a week he continued to look as if he were going to die within the next twenty-four hours. Then he became better and more alert. After that he developed queer herpetic lesions. There was some question whether they were herpes or were due to monilia infection secondary to the aureomycin that he had received. He had a queer skin lesion on the right flank — a necrotic eschar in the center with induration around it in an elliptical area about 3 by 7 cm. The nature of this was quite puzzling.

We thought, Dr. Brailey, that the guaiac-positive stools were due to blood that he swallowed after the nosebleed. The prothrombin time was considerably less. When the jaundice began to fall and the cephalin-flocculation test, which had been ++++, became ++, we wondered whether he had an acute vascular insult to the liver or to the mesentery and the liver. Diagnoses of mesenteric thrombosis and of hepatic-vein thrombosis were entertained. In that way we thought we might explain the severe insult and parenchymal damage to the liver and the subsequent improvement. As the disease progressed we gave up the idea that he had a common-duct stone, because the jaundice disappeared clinically and by chemical test was only minimal. The stools became yellow and contained bile. The urine also contained bile. At one moment the patient looked as if he were going to get well and at the next he was moribund. That was difficult to explain. In the last few days of his illness we were wondering whether he had a brain abscess, intracranial bleeding subsequent to the low prothrombin time at the time of admission or tumor. The nonprotein nitrogen fluctuated in spite of perfectly adequate urinary output; that was difficult to explain. At the time of death we thought that he had a cholangitis and an *E. coli* septicemia. We did not think he had cholecystitis.

Dr. Tracy B. Mallory: The x-ray impression as given in the protocol did not sound particularly interesting. Did you see anything in the films?

Dr. Ellis: The x-ray films did not help us. We thought he had pneumonia in the left lower lobe at the time of admission. He had persistent diminished breath sounds and rales in the left lower lobe throughout the hospital course. However, the x-ray films were unsatisfactory because of the severe degree of illness.

Clinical Diagnoses

Hepatic-vein thrombosis with cholemia and uremia.
?Cerebral hemorrhages.
E. coli septicemia.
Cholangitis.
Generalized arteriosclerosis.

Dr. Brailey's Diagnoses

Biliary obstruction due to stone.
Sepsis, probably of gall bladder or liver.
?Pancreatitis.
Arteriosclerotic heart disease.

Anatomical Diagnoses

Choledocholithiasis with obstruction of main hepatic duct and extension into common duct.
Cholangitis with abscess formation in left lobe of liver.
Calcification of head of pancreas.

Pathological Discussion

Dr. Mallory: We did not have permission to examine the head in this case, hence I cannot tell you whether there was or was not intracranial disease, but symptoms such as he presented are not unusual in a considerable variety of liver diseases. It was rather impressive, in reviewing a series of cases of fatal hepatitis in Army hospitals, to find that at least three patients had entered the hospital on the Neurosurgical Service and had at least a lumbar puncture — and in one instance a cranial exploration for a subdural hematoma.

The most obvious finding at autopsy was a gallstone. It lay at the junction of the hepatic and cystic ducts and extended a short distance into the common bile duct, a strategic location that would not only have prevented bile from passing down normal channels to the intestine but would also have occluded the cystic duct so that the cholecystenterostomy would no longer have provided drainage to the biliary system. The gall bladder was small and had somewhat thickened walls. The appearance suggested prolonged chronic inflammation. There was no evidence of tumor, and the stoma between the gall bladder and jejunum was still patent, indicating that the cholecystojejunostomy must have continued to function until very near the end of the clinical course. In the left lobe of the liver several small abscesses ranging from 1 to 1.5 cm. were found. There was no thrombophlebitis in either the portal- or hepatic-vein radicles. One other finding was a large focus of necrosis with calcification in the head of the pancreas. I know of no reason that previous pancreatitis should not have been responsible for the calcification, inasmuch as it is characteristically associated with fat necrosis. A splitting of neutral fats, with liberation of fatty acids, is a common precursor of calcification. The other findings at autopsy seemed coincidental and not very important in relation to the man's symptomatology. There was a terminal bronchopneumonia, and he had about the amount of atherosclerosis that might be expected in an average person seventy-four years of age.

Dr. Brailey: Was the common duct distal to the stone normally patent?

Dr. Mallory: It not only was patent but appeared dilated. It is very difficult, from observing a stone in the common duct at the time of autopsy, to decide whether or not it has been causing obstruction, as so much would depend on the tonicity of the muscular walls of the duct about the stone.

Dr. Brailey: Isn't it true that the fact that the cholecystojejunostomy was still present argues that the normal channel was not? My impression has been that if the original obstruction is removed the operative channel closes up, as a rule.

Dr. Mallory: That is what one expects.

Dr. Ellis: The cholecystojejunostomy was still open. We had no trouble in passing a probe down the common duct. The left hepatic duct had been obstructed for so long that all the ducts in the liver were dilated. It was hard to see how any bile had gone by the stones, which were up in the porta hepatis. Why the jaundice was severe although there was bile in the stools must have been, as Dr. Mallory explained, due to spasm that had caused complete obstruction and then was released. It is interesting to speculate on the cause of the trouble thirty-six years before entry. Dr. John W. Raker suggested that perhaps the stone was slipping up and down in the common duct. The one thing against that is that the stones were molded in the position in which they were found and looked as if they had been lying there for a long time. I wondered whether he had a stone in the distal common duct when he was explored thirty-six years prior to entry and whether it had eventually moved back up to the porta hepatis.

CASE 37382

Presentation of Case

First admission. A forty-four-year-old man entered the hospital because of shortness of breath. For three years prior to admission the patient had noted slight exertional dyspnea and increasing fatigability. After an operation nine months before admission (allegedly a ligation of a left aberrant renal blood vessel for hematuria), he developed increasing dyspnea with ankle and leg edema. He also noted palpitations, pulsations in the neck and an occasional dizzy spell. Eight months before entry he was admitted to another hospital for eleven days. He was treated with "pills" and the edema gradually disappeared. This did not recur, even though he soon stopped the medication. One month before entry there was an episode of sharp pressure over the lower sternum that lasted only a few minutes. Exertional dyspnea remained moderately severe and prevented his return to work.

At the age of twenty-four he had had lobar pneumonia. A duodenal ulcer was diagnosed by x-ray examination at the age of forty-one. For several years he had had frequent severe upper-respiratory infections during the winter. For six years prior to admission he was in contact with zinc dust and naphthol in his work.

His mother died of "heart disease" at the age of fifty; one sister died at the age of forty-six of "complete atrio-ventricular block with right bundle branch block and findings consistent with coronary thrombosis."

On physical examination the neck veins were distended and pulsating to the angle of the jaw in the upright position. The anteroposterior diameter of the chest was greatly increased with only slight inspiratory expansion. There were decreased breath sounds and tactile fremitus with dullness at the right base and to a lesser extent at the left base, and intermittent rales posteriorly in both lung fields. The heart was markedly enlarged, with the point of maximal impulse between the anterior and midaxillary lines. The rhythm was regular and there were no murmurs or thrills. The liver and spleen were not palpable. There was slight ankle edema.

The pulse was 56 and the temperature 98.3°F. The blood pressure was 100 systolic, 65 diastolic.

Urinalysis and a stool guaiac test were negative. Examination of the blood showed a hemoglobin of 12 gm. and a white-cell count of 4200, with a normal differential. The nonprotein nitrogen was 24 mg. and the total protein 6.5 gm. per 100 cc. The vital capacity was 1.8 liters (corrected for weight), or 44 per cent of normal. The circulation time (Decholin) was 23 seconds. The blood Hinton test was negative. Venous pressures in the right antecubital and femoral veins above the angle of Louis were equivalent to 200 mm. of saline solution. An x-ray film of the chest showed generalized cardiac enlargement, with a contour suggesting enlargement of the left auricle, right ventricle, right auricle and probably also the left ventricle. The aorta was somewhat elongated. There was elevation of the right leaf of the diaphragm and a small amount of pleural fluid within the right chest (Fig. 1). An electrocardiogram showed a normal rhythm of 54, a PR interval of 0.20 second, a QRS interval of 0.13 second and a left-bundle-branch block.

FIGURE 1.

In the hospital the patient responded slightly to mercurial diuretics and was discharged on digitalis and diuretics after seven hospital days.

Second admission (three months later) because of weakness of the left leg for one day.

Since his previous admission the patient had been followed in the medical Out Patient Department. He was digitalized, but this was discontinued because of bradycardia and ventricular premature beats. He was also treated with Mercuhydrin, ammonium chloride and a low-salt diet. On this regimen he continued to show moderate exertional dyspnea, two-pillow orthopnea and occasional ankle edema. On the day before admission, while painting on a ladder, he suddenly fell because of weakness in the left arm and leg. He did not lose consciousness, and there were no convulsions or incontinence, but he noted a slight frontal headache.

On physical examination there was evidence of weakness of the fifth, seventh, ninth, twelfth and questionably of the eleventh cranial nerves on the left. The left pupil was larger than the right, and there was a partial flaccid paralysis of the left arm and leg and a positive left Babinski sign. Otherwise physical findings were similar to those found at the first admission.

The blood pressure was 100 systolic, 75 diastolic.

Examination of the blood showed a hemoglobin of 15 gm. and a white-cell count of 7300. Lumbar puncture revealed normal cerebrospinal-fluid pressure, dynamics and chemical findings. There were no cells in the fluid. Venous pressure in the right arm was equivalent to 150 mm. saline solution (corrected) and the circulation time was 36 seconds. An electrocardiogram was unchanged.

By the tenth hospital day he had completely recovered from the left-sided paralysis. On digitalis, ammonium chloride, Mercuhydrin and a low-salt diet he improved somewhat, both subjectively and objectively, and was discharged on the twelfth hospital day to continue on this regimen.

Final admission (five months later). Since discharge the patient had been doing very well on the prescribed regimen. Three days before admission the patient was found unconscious at the wheel of his automobile at the side of a road. He was taken to another hospital, where without specific treatment he regained consciousness after forty-eight hours. He was able to follow simple commands but was aphasic and unable to swallow. He was transferred to this hospital twenty-four hours later.

Physical examination revealed a semicomatose man. There was a right-facial paralysis. The pupils were equal. Deep tendon reflexes were hyperactive on the right, with ankle clonus. There was complete

loss of sensory and motor power in the right arm and leg. There was dullness to percussion of the lower half of the right chest, both anteriorly and posteriorly. Breath sounds here were bronchovesicular and in the remainder of the lung were distant, with many coarse rales. The cardiac impulse was at the left anterior axillary line. There were no murmurs, friction rubs or gallop. The abdomen was normal.

The temperature was 103°F., the pulse 60 and the respirations 54. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis showed a specific gravity of 1.027 and the presence of bile on foam test. Examination of the blood revealed a hemoglobin of 13.5 gm. and a white-cell count of 11,200, with 72 per cent neutrophils. The serum bilirubin was 2.4 mg. direct, 4.8 mg. total, the nonprotein nitrogen 43 mg. and the total protein 6.12 gm. per 100 cc. with an albumin-globulin ratio of 1.60; the prothrombin time was 25 seconds (normal, 17 seconds) and the cephalin flocculation ++ in 24 and 48 hours. Lumbar puncture revealed that the spinal fluid was under a normal pressure and contained 5 red cells per cubic mm. and 56 mg. per 100 cc. of protein. An electrocardiogram showed an irregular rhythm at a rate of 70, with a PR interval varying from 0.10 to 0.34 second and a QRS interval of 0.16 second. There was left-bundle-branch block. On the third day the electrocardiogram showed auricular fibrillation at a rate of 45 with a QRS interval of 0.14 second but otherwise no change. X-ray films of the chest showed fluid in the right pleural space. The vessels were prominent throughout both lung fields and the heart was greatly enlarged without characteristic configuration, the enlargement being probably greater than on previous examinations.

The patient was treated with intravenous fluids, Crysticillin, streptomycin, Mercuhydrin and digitalis. There was gradual improvement on this regimen, until by the fifth hospital day the temperature was normal and the patient was a little more alert, although the paralysis persisted. His condition slowly deteriorated, with a gradually rising temperature, severe dyspnea, cyanosis and hypotension. He died quietly on the twelfth hospital day.

Differential Diagnosis

Dr. Gordon Myers*: This patient's present illness began, as nearly as can be gathered from the record, when he was forty-one years old, with dyspnea followed by edema, palpitations and spells of dizziness. It seems to me that there can be no doubt that the illness and ultimate death resulted from some form of heart disease with congestive failure. Certainly all the evidence from the physical examination, laboratory data and x-ray findings support that idea. On physical examination the heart was markedly enlarged; the neck veins were distended; rales were heard over both lung fields and there was ankle edema. In addition, the physical examination suggested that the patient had emphysema: the anteroposterior diameter of the chest was said to be large and there was very little expansion of the thorax with inspiration. The laboratory data indicated a reduced vital capacity, a prolonged circulation time and increased venous pressure. The electrocardiograms, some of which I have seen, showed left-bundle-branch block, first with sinus bradycardia and later with auricular fibrillation. There was no clear evidence of myocardial infarction in the records that I saw. The x-ray films were interpreted as indicating enlargement of the left auricle, right ventricle, right auricle and probably the left ventricle — in other words, generalized enlargement of the heart. Later there were signs of increasing pulmonary vascular markings and more pronounced enlargement of the heart. May I see the x-ray films at this point?

Dr. Joseph Hanelin: We have chest films extending over a period of seventeen months. The thorax is large and barrel shaped and the anteroposterior diameter is very close to the transverse measurement. Although there is probably some degree of emphysema this cannot be marked because of the relatively high position of the diaphragm. The right leaf is elevated more than the left and the right costophrenic sulcus is obliterated. This could be the result of scarring from previous infarction. There is very likely no free pleural fluid. The heart is enlarged, predominantly on the right (Fig. 1). The films at the last admission when the patient was preterminal were not made under ideal conditions: the patient was supine. There is increased density of the right thorax owing most likely to a collection of pleural fluid. It is difficult to be sure whether or not further heart enlargement has occurred.

Dr. Myers: Are pulmonary vascular markings increased on the last film?

Dr. Hanelin: Slightly.

Dr. Myers: Why do you think the right dome of the diaphragm is high? Is the liver enlarged?

Dr. Hanelin: We have no clear-cut evidence that it is enlarged.

Dr. Myers: Do you think there was any atelectasis in the right lung?

Dr. Hanelin: I rather doubt that. Some of the change in density may be due to obesity and some to pleural fluid.

Dr. Myers: I am afraid the x-ray findings do not help me a great deal. The questions are: What kind of heart disease did this patient have, and what was the nature of the serious cerebral complications that occurred? There are some common conditions that this patient probably did not have. There were no heart murmurs; therefore I can rule out any kind of valvular heart disease. There was no history of hypertension and none was noted dur-

*Assistant physician, Massachusetts General Hospital.

ing any of the episodes that brought the patient to the hospital; therefore I cannot make a diagnosis of hypertensive heart disease. In regard to the possibility of cor pulmonale, the patient had emphysema of a considerable degree and did have a reduced vital capacity, which may have been caused by pulmonary disease, but the clinical picture in this patient was not like that in the usual case of cor pulmonale. The history of three years of mild to moderate dyspnea was too short to account very well for severe pulmonary disease leading to congestive failure. The patient never showed clubbing or cyanosis. Arrhythmias are certainly uncommon in cases of cor pulmonale, including bundle-branch block, unless other types of heart disease are present in addition. I do not believe this patient had cor pulmonale, although there seems to be no doubt that he had emphysema. If he had any degree of cor pulmonale, I think there must have been another more important complication.

Other conditions in which no heart murmurs are heard include a peripheral arteriovenous aneurysm or constrictive pericarditis, but there was no evidence for either of these lesions. Arrhythmias are common enough in constrictive pericarditis, but I should expect to find some evidence of calcification about the heart and would not expect a serious cerebral complication.

I suppose it is necessary to list briefly some of the uncommon causes of heart disease and congestive failure. This patient was exposed to zinc and naphthol. So far as I know these agents do not cause chronic pulmonary disease or chronic heart disease. We know that naphthol, — beta naphthelamine, — may be responsible for bladder irritation and may even predispose to carcinoma of the bladder. I suppose it is possible that the hematuria could have been on such a basis, but there was no clear evidence in that direction. How about tumors of the heart, primary or metastatic? If metastatic, from where — the gastrointestinal tract? Apparently the patient was thought to have an ulcer of the duodenum. He had hematuria in the past, but there was no further bleeding, and the stools were guaiac negative. I cannot make a diagnosis of tumor of the heart, which is, of course, a rare condition. The patient did not have an anemia. There was no avitaminosis. There was no history of trauma and no evidence of hemochromatosis or sarcoidosis that I can see. One always has to think of the obscure possibility of one of the connective-tissue diseases — scleroderma, lupus erythematosus or polyarteritis. One always hesitates to mention polyarteritis at these conferences; it is usually brought up as a last resort. There was probably a lesion in the duodenum, and the patient did have blood in his urine, cerebral episodes and heart disease, so one cannot rule the diagnosis out.

Primary amyloidosis is another very rare condition that can lead to congestive heart failure; often such patients have congestive failure as the chief cause of death. The disease may also affect the smooth muscles of the gastrointestinal tract and blood vessels everywhere, including the brain. However, patients with primary amyloidosis frequently show macroglossia, which was not mentioned in this case, and cerebral complications are rare, so I do not seriously consider that diagnosis here.

Finally I come to several ill defined conditions of unknown etiology that I do not think it worth while to classify exhaustively. Cardiac hypertrophy of unknown cause occurs in adults as well as in children. Its chief clinical features are myocardial insufficiency with congestive failure; arrhythmias, including bundle-branch block; and occasional abdominal pain — but anginal pain is notably absent. Physical examination does not show heart murmurs, and the blood pressure is low or normal. Emboli from mural thrombi are rather common.

Another set of conditions is included under myocarditis. Apparently myocarditis has been described as complicating almost every known type of infection, virus or otherwise. On the other hand, the disease may be of unknown cause. The patient had no history of infection. Sometimes myocarditis has a familial incidence. This patient's mother and sister died of heart disease at an early age. Patients with myocarditis may have this sort of clinical course and may show embolic phenomena.

Finally, a most common condition is coronary heart disease. Patients with coronary heart disease, with or without myocardial infarction, may show congestive heart failure as the primary symptom. They may never have anginal pain. This patient had a brief episode of pain, but it was not characteristic of a myocardial infarction. If he had coronary heart disease with a myocardial infarction the electrocardiogram might not help very much because in the presence of bundle-branch block it is difficult or sometimes impossible to diagnose a myocardial infarction. Emboli to the kidney and brain would be well accounted for if mural thrombi were present in the heart. The family history of heart disease would go perfectly well with coronary heart disease as well as with myocarditis. Certainly it can occur at this age — 200 proved cases of coronary heart disease and myocardial infarction in patients under the age of forty have been studied in this hospital.

Immediately before death there seems to have been evidence of liver impairment and some elevation, though slight, of the nonprotein nitrogen. I am sure that those findings could be accounted for by congestion of the liver due to heart failure, although one would expect to find liver enlargement by physical examination. The final episode was probably bronchopneumonia or possibly pulmonary emboli.

I have no great confidence in any diagnosis I am going to make, as I have already indicated. I think I shall put down as my first bet idiopathic hypertrophy or myocarditis of unknown cause, possibly familial in this case, and, as a very close second, coronary heart disease with myocardial infarction. I think the patient showed evidence of congestive heart failure, emboli to the brain from mural thrombi in either the auricle or the ventricle, perhaps an old infarction of the kidneys to account for the hematuria for which the operation was performed, emphysema and possibly bronchopneumonia and perhaps a healed duodenal ulcer.

Clinical Diagnoses

Myocarditis.
?Subendocardial fibrosis.
Bronchopneumonia.
Cerebrovascular accident.

Dr. Myers' Diagnoses

Idiopathic hypertrophy or myocarditis of unknown cause.
?Coronary heart disease with myocardial infarction.
Congestive heart failure.
Emboli to brain.
Old infarct of kidneys.
Probable bronchopneumonia.
?Pulmonary emboli.

Anatomical Diagnoses

Idiopathic cardiac hypertrophy with subendocardial and myocardial fibrosis.
Cerebral and renal infarcts, old and recent.
Bronchopneumonia.

Pathological Discussion

Dr. Tracy B. Mallory: At autopsy the patient was found to have a hypertrophied heart (450 gm.) with normal valves and normal coronary arteries. The most obvious changes in the heart were patches of thickening of the endocardium and of the underlying myocardium of rather dense fibrous scars. I have a picture representing a segment of the left ventricle (Fig. 2). This case did not seem to fit clearly, as Dr. Myers suggested, into any of the well defined entities or types of heart disease. Microscopical examination of the heart showed no progressive inflammatory or degenerative changes in the myocardium. It seemed to fit most closely with a group of cases described by Smith and Furth[1] from the New York Hospital, in which the most obvious lesion was subendocardial fibrosis occurring sometimes in the left and sometimes in the right ventricle, associated with a marked tendency to mural thrombus formation and episodes of embolism. One of their patients had pellagra, and they raised the question whether the cardiac changes were related to a deficient diet and represented a variant of the beri-beri heart. Dr. Myers apparently agrees with Levy and von Glahn,[2] who prefer to include these cases in the condition known as cardiac hypertrophy of unknown cause, or idiopathic cardiac hypertrophy, examples of which we are now seeing with increased frequency. Admittedly this is a wastebasket for cases of cardiac hypertrophy of different unknown etiologies, but perhaps when enough cases have been collected some of them will fall into

Figure 2.

separate categories. This case seems to differ from the usual cases of so-called isolated or Fiedler's myocarditis in that involvement of the myocardium is much less conspicuous than that of the subendocardial tissues — also, the tendency toward embolic complications seems to be considerably greater. One feature that struck me as unusual in this case was that many of the areas of scarring contained numerous large, well formed fat or adipose cells. An extension of adipose tissue from the epicardium downward through the right ventricle is relatively common in elderly patients, particularly in association with obesity. Whether that is a cause of functional impairment of the heart and really deserves to be considered a pathologic lesion I am uncertain, although it is my impression that we have seen rather numerous instances of sudden death in which no other explanation could be found.

Other findings of significance were a bronchopneumonia, presumably terminal, an old healed infarction of the kidney and multiple foci of infarction of the cerebral cortex.

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PENSIVE CITADELS

THE late Admiral Forrest Sherman is said to have advised a sister that too great a personal popularity must be avoided by the student who wishes to achieve any considerable academic distinction. The obvious inference was that any noticeable degree of social success is generally incompatible with the fulfillment of a more substantial ambition.

This familiar observation does not necessarily underscore any invariable rule, for there are those gifted persons who seem able to direct their great talents into quite dissimilar channels at the proper times; but by and large solitude is the medium in which the most abundant growth takes place.

The uses of solitude and of social unworldliness were suggested by Wordsworth in the opening lines of his sonnet in praise of the sonnet:

> Nuns fret not at their convent's narrow room;
> And hermits are contented with their cells.
> And students with their pensive citadels; —

Santayana, also, willing to finish his long life in a convent's narrow room, was responsible for the lines:

> A wall, a wall around my garden rear
> And shut me off from the disconsolate hills.

It may be assumed that these particular poets found solitude rather cozy.

One need not be frustrated, therefore, in order to develop a dogged determination to go places, but it helps, as the government employe said when asked if three cups of coffee did not keep him awake.

The desire for achievement and the consciousness of a personal destiny are not necessarily mechanisms to compensate for some deficiency elsewhere in the personality or for a real or imagined lack of opportunity, but the fact remains that the most successful efforts are usually made in the face of obstacles. Lincoln's eventual triumph as a leader followed repeated attempts after repeated failures, and his was a lonely soul despite his well known sense of humor.

This same fierce urge to overcome persistent handicaps is shown in the life of Samuel Johnson, whose physical illnesses and emotional difficulties have been admirably summarized in a paper by Peter Pineo Chase,* the scholarly editor of the *Rhode Island Medical Journal*. The child of an elderly primipara, anoxic at birth, scrofulous, partly deaf and partly blind and subject to melancholy, the great lexicographer, unhampered by youthful social temptations, found freedom to develop his knowledge and his talents.

Dr. Chase presents an imposing list of adverse conditions under which Dr. Johnson had to take what comfort he could:

> Severe trauma and anoxia at childbirth; early infection with bovine tuberculosis, involving the cervical glands and possibly the eye; loss of function of the left ear, possibly due to birth trauma, possibly to smallpox; skin-scarring due to smallpox; cerebral irritation through life, the aftermath of birth injuries; chronic bronchitis, possibly some allergic asthma resulting in emphysema;

*Chase, P. P. Ailments and physicians of Dr. Johnson. *Yale J. Biol. Med.* 23:370-379, 1951.

hypertension due largely to cystic degeneration of the kidney; cerebral thrombosis; hydrocele; his terminal condition, cardiorenal disease.

"A poor start at birth," Chase notes elsewhere, "scrofulous, half blind, deaf, disfigured features, unable to continue at Oxford, poor as a church mouse, a failure at teaching — he had reason to be melancholic." He had reason also to strive for the hidden manna that is given to him that overcometh. It was only in his later life that Johnson became the dictator of the Club, and the Club was rather a meeting of minds than a medium of purely social intercourse.

It is not as herd animals, giving play to their gregarious instincts, that men make their greatest contributions to that complex organization called society; and those who make the greatest contributions to it often do so at the cost of their own share in its amenities. One is reminded of Mrs. Browning's lines, with their hint of personal sacrifice:

> Yet half a beast is the great god Pan,
> To laugh as he sits by the river,
> Making a poet out of a man:
> The true gods sigh for the cost and pain —
> For the reed which grows nevermore again
> As a reed with the reeds of the river.

A BUBBLE BURSTS: THE PELS-MACHT TEST IN PEMPHIGUS

Pemphigus is one of many diseases of unknown etiology in which a "toxic" origin has been postulated. In 1929 Pels and Macht[1] proposed a test that was alleged to detect a toxin in the serum of patients with this disease. The test depends on the demonstration of inhibition of growth of *Lupinus albus* seedlings when immersed in a 1 per cent solution of blood serum and is generally known as the phytopharmacologic test for pemphigus. Macht claims to have demonstrated a similar phytopharmacologic activity in the serum of patients with a wide variety of conditions varying from menstruation in normal women to pernicious anemia and general paresis.

Although this test has been quoted by many workers and its diagnostic relation to pemphigus has frequently been mentioned, there have been few serious attempts to evaluate the test in cases of pemphigus. Hollander and Greb[2] in 1936 failed to confirm Macht's findings in a small number of cases.

Recently Baldridge and Kligman, in the Department of Dermatology and Syphilology of the University of Pennsylvania, reported the results of their attempts to demonstrate a toxic factor in the serums of patients with pemphigus.[3] In addition to tests for inhibition of growth of *L. albus* as carried out by Pels and Macht, the Philadelphia workers tested the serums of patients with pemphigus for their ability to inhibit the germination of the macroconidia of *Microsporum fulvum*, one of the ringworm organisms. They also subjected these serums to more delicate tests for toxin, namely, the inhibition of proliferation of embryonic fibroblasts and of human leukocytes in tissue cultures. These workers were unable to confirm the results of Pels and Macht. The growth of *L. albus* seedlings was not inhibited, nor was the germination of *M. fulvum* spores interfered with by the presence of pemphigus serums. The proliferation of chick-embryo fibroblasts and the migration of human leukocytes also were not interfered with by the serums of pemphigus patients.

References

1. Pels, I. R., and Macht, D. I. Phytopharmacologic examination of blood in pemphigus and in some other diseases of skin. *Arch. Dermat. & Syph.* 19:640-650, 1929.
2. Hollander, L., and Greb, R. J. Evaluation of phytopharmacologic test of Pels and Macht: further report. *Arch. Dermat. & Syph.* 34: 650-655, 1936.
3. Baldridge, G. D., and Kligman, A. M. Critical evaluation of toxicity of pemphigus serum (Pels-Macht test). *J. Lab. & Clin. Med.* 38: 128-132, 1951.

RHODE ISLAND LEADS

The indefatigable statisticians of the Metropolitan Life Insurance Company, having uttered the latest (if not the last) word on marriage, have, perhaps by a simple association of ideas, turned their attention to the statistical risks of being struck by thunderbolts.

Approximately 250 Americans meet their end each year by lightning but not, according to the statisticians, in Rhode Island. This state, with its aptly named capital city, is the safest place in the country to live, so far as lightning is concerned, for Rhode Island has not recorded a death from this cause since 1936.

Perhaps a reason for this comparative immunity is the relatively dense population of the state, which lives largely in cities and towns where pro-

tection is at its maximum, for steel-skeletoned buildings act as lightning rods, and adequate shelters are easily available. Figures indicate, as a matter of fact, that 9 out of 10 fatalities from lightning occur in places with 2500 inhabitants or less.

Exposed areas are the most dangerous ones in which to be caught by a thunderstorm. This applies to open fields and open water, whether one is on it, as in a small boat, or in it, as in swimming. The metal bodies of automobiles offer such effective protection that the mortality in America could conceivably be reduced to zero. Four times as many men as women are killed by lightning, a fact that possibly supplies the missing link, if any, between electrocution and the connubial state.

. . . but as a wound cannot be healed by the perpetual application of rubefacients, so neither can an irritable mind be calmed by unceasing vollies of vituperation.

Boston M. & S. J., *September 24, 1851*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 3, at 10:30 a.m. This meeting will be followed by the Cotting Luncheon.

Business:

1. Presentation of record of meeting held May 21, 1951, as published in *Supplement No. 1*, August 9, 1951.
2. Reports of standing and special committees.
3. Such other business as may legally come before the meeting.

H. Quimby Gallupe, M.D., *Secretary*

DEATH

Worcester — Alfred Worcester, M.D., of Waltham, died on August 28. He was in his ninety-seventh year.

Dr. Worcester received his degree from Harvard Medical School in 1883. He was Oliver Professor of Hygiene at Harvard Medical School from 1925 to 1935. He was a former president of the Massachusetts Medical Society, the Boston Obstetrical Society and the Harvard Medical Alumni Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONFERENCE ON PROPOSED HEALTH LEGISLATION

A conference will be held on September 27, from 3 to 5 p.m., in the Gardner Auditorium, State House, to consider bills on health matters to be introduced at the next annual session of the General Court or at succeeding sessions.

This annual conference has been held in the fall for several years under the auspices of the Massachusetts Central Health Council and the Massachusetts Department of Public Health. Representatives of civic organizations and interested citizens are welcome at the conference.

Proposed bills to be considered at the conference should be forwarded to Mr. C. W. Kammeier, executive secretary of the Massachusetts Central Health Council. Suggestions for proposed legislation are welcomed from any person who believes that our health laws should be amended or that new statutes should be added.

The Massachusetts Medical Society is one of the constituent organizations in the Central Health Council. Representatives of the Society have regularly attended these conferences, but all interested physicians should also attend — to participate in the discussions or to learn the background of proposed legislation.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The October schedule for Consultation Clinics for Crippled Children in Massachusetts follows:

Orthopedic Clinics	Date	Clinic Consultant
Salem	October 1	Paul W. Hugenberger
Haverhill	October 3	William T. Green
Greenfield	October 4	Charles L. Sturdevant
Lowell	October 5	Albert H. Brewster
Lynn*	October 8	Daniel M. Killoran John J. Crowley
Gardner	October 9	Carter R. Rowe
Brockton	October 11	George W. Van Gorder
Springfield	October 16	Garry deN. Hough, Jr.
Pittsfield	October 17	Edward J. Coughlin, Jr.
Worcester	October 19	John W. O'Meara
Fall River	October 22	David S. Grice
Hyannis	October 25	Paul L. Norton

Rheumatic Fever Clinics	Dates
North Reading	October 2, 9, 16, 23, 30
Fitchburg	October 3, 10, 17, 24, 31

Plastic Clinics	Consultant
Eastern Massachusetts	Bradford Cannon Semi-monthly
Western Massachusetts	Joseph M. Baker Monthly

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

(*Notices on page xvii*)